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(54) Title: UREA SUBSTITUTED IMIDAZOPYRIDINES

(57) Abstract: Imidazopyridine compounds that contain urea or thiourea functionality at the 1-position are useful as immune response modifiers. The compounds and compositions of the invention can induce the biosynthesis of various cytokines and are useful in the treatment of a variety of conditions including viral diseases and neoplastic diseases.

Urea Substituted Imidazopyridines

Field of the Invention

5 This invention relates to imidazopyridine compounds that have urea or thiourea functionality at the 1-position, and to pharmaceutical compositions containing such compounds. A further aspect of this invention relates to the use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals, and in the treatment of diseases, including viral and neoplastic diseases. The invention also provides methods of
10 making the compounds and intermediates useful in their synthesis.

Background of the Invention

 The first reliable report on the 1*H*-imidazo[4,5-*c*]quinoline ring system, Backman et al., *J. Org. Chem.* 15, 1278-1284 (1950) describes the synthesis of 1-(6-methoxy-8-quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline for possible use as an antimalarial
15 agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*]quinolines were reported. For example, Jain et al., *J. Med. Chem.* 11, pp. 87-92 (1968), synthesized the compound 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline as a possible anticonvulsant and cardiovascular agent. Also, Baranov et al., *Chem. Abs.* 85, 94362
20 (1976), have reported several 2-oxoimidazo[4,5-*c*]quinolines, and Berenyi et al., *J. Heterocyclic Chem.* 18, 1537-1540 (1981), have reported certain 2-oxoimidazo[4,5-*c*]quinolines.

 Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and
25 immunomodulators. These are described in, *inter alia*, U.S. Patent Nos. 4,689,338; 4,698,348; 4,929,624; 5,037,986; 5,268,376; 5,346,905; and 5,389,640.

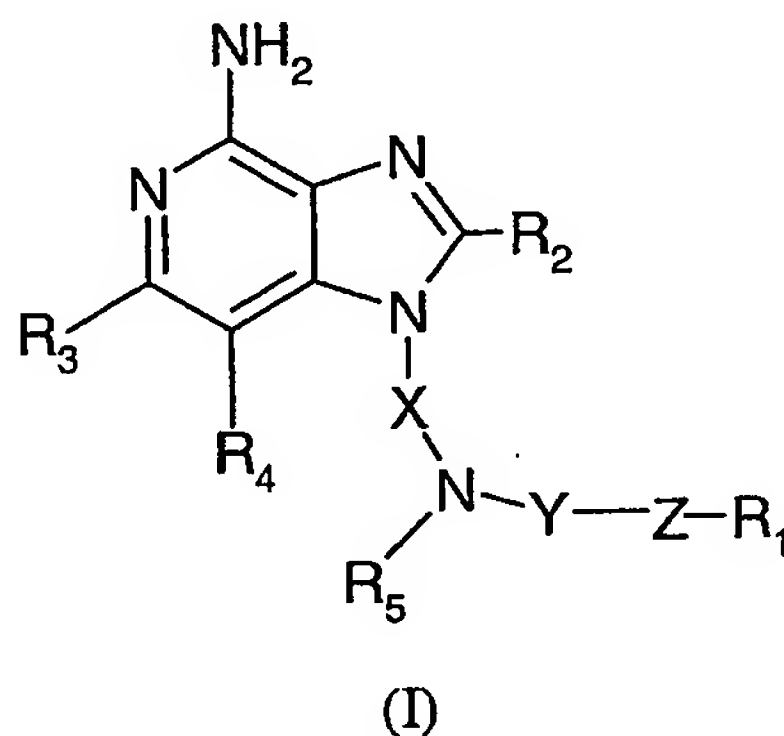
 Substituted 1*H*-imidazopyridine-4-amine compounds useful as immune response modifiers are described in United States Patent Nos. 5,446,153; 5,494,916; and 5,644,063. The compounds described in these patents do not have amine containing substitution at the
30 1- position. Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines that have amide, sulfonamide, and urea functionality at the 1-position are described in PCT Publications WO 00/76505,

WO 00/76518 and U.S. Patent No. 6,331,539. All of the above-mentioned patents and published patent applications are incorporated herein by reference.

Despite these recent discoveries of compounds that are useful as immune response modifiers, there is a continuing need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

Summary of the Invention

We have found a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Accordingly, this invention provides imidazopyridine-4-amine compounds that have urea or thiourea functionality at the 1-position. The compounds which have been found to be useful inducers of cytokine biosynthesis are defined by Formula (I), which is described in more detail *infra*. Formula (I) is as follows:



wherein X, Y, Z, R₁, R₂, R₃, R₄, and R₅ are as defined herein.

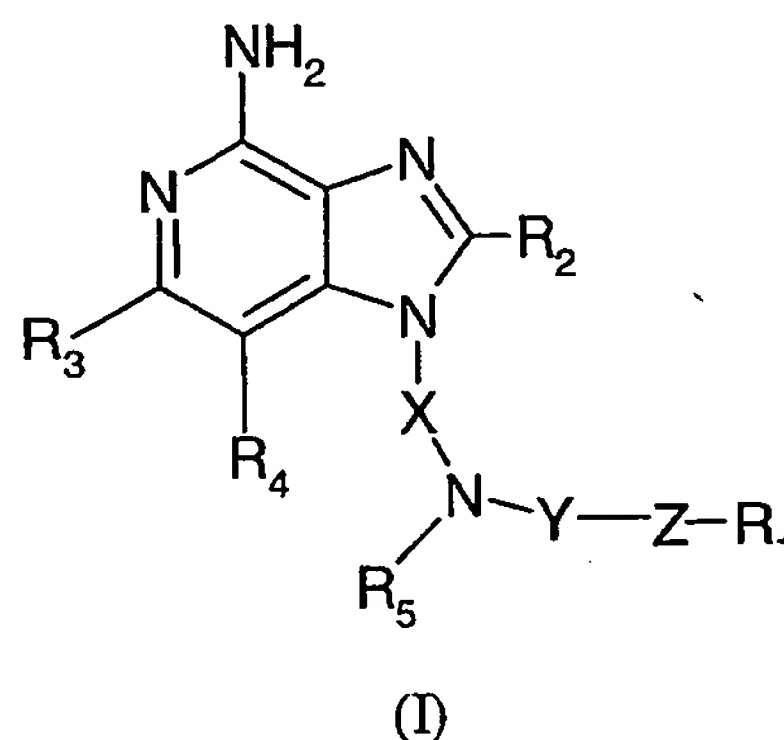
The compounds of Formula (I) are useful as immune response modifiers due to their ability to induce cytokine biosynthesis and otherwise modulate the immune response when administered to animals. This makes the compounds useful in the treatment of a variety of conditions such as viral diseases and tumors that are responsive to such changes in the immune response.

The invention further provides pharmaceutical compositions containing the immune response modifying compounds, and methods of inducing cytokine biosynthesis in an animal, treating a viral infection in an animal, and/or treating a neoplastic disease in an animal by administering a compound of Formula (I) to the animal.

In addition, the invention provides methods of synthesizing the compounds of the invention and intermediates useful in the synthesis of these compounds.

Detailed Description of the Invention

As mentioned earlier, we have found that certain compounds induce cytokine biosynthesis and modify the immune response in animals. Such compounds are represented by Formula (I) below:



wherein

X is alkylene or alkenylene;

Y is $-\text{CO}-$ or $-\text{CS}-$;

Z is $-\text{NR}_6-$; $-\text{NR}_6-\text{CO}-$; $-\text{NR}_6-\text{SO}_2-$; or $-\text{NR}_7-$;

R₁ is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-substituted aryl;

-substituted heteroaryl;

substituted heterocyclyl;

-O-alkyl;

- 5
- O-(alkyl)₀₋₁-aryl;
 - O-(alkyl)₀₋₁-substituted aryl;
 - O-(alkyl)₀₋₁-heteroaryl;
 - O-(alkyl)₀₋₁-substituted heteroaryl;
 - O-(alkyl)₀₋₁-heterocyclyl;
 - O-(alkyl)₀₋₁-substituted heterocyclyl;
 - COOH;
 - CO-O-alkyl;
 - CO-alkyl;
- 10
- S(O)₀₋₂-alkyl;
 - S(O)₀₋₂-(alkyl)₀₋₁-aryl;
 - S(O)₀₋₂-(alkyl)₀₋₁-substituted aryl;
 - S(O)₀₋₂-(alkyl)₀₋₁-heteroaryl;
 - S(O)₀₋₂-(alkyl)₀₋₁-substituted heteroaryl;
- 15
- S(O)₀₋₂-(alkyl)₀₋₁-heterocyclyl;
 - S(O)₀₋₂-(alkyl)₀₋₁-substituted heterocyclyl;
 - (alkyl)₀₋₁-N(R₆)₂;
 - (alkyl)₀₋₁-NR₆-CO-O-alkyl;
 - (alkyl)₀₋₁-NR₆-CO-alkyl;
- 20
- (alkyl)₀₋₁-NR₆-CO-aryl;
 - (alkyl)₀₋₁-NR₆-CO-substituted aryl;
 - (alkyl)₀₋₁-NR₆-CO-heteroaryl;
 - (alkyl)₀₋₁-NR₆-CO-substituted heteroaryl;
 - P(O)(Oalkyl)₂;
- 25
- N₃;
 - halogen;
 - haloalkyl;
 - haloalkoxy;
 - CO-haloalkyl;
- 30
- CO-haloalkoxy;
 - NO₂;
 - CN;

-OH;

-SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R₂ is selected from the group consisting of:

5

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-substituted aryl;

10

-heteroaryl;

-substituted heteroaryl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

15

-alkyl-S-aryl;

-alkyl-O-alkenyl;

-alkyl-S-alkenyl; and

-alkyl or alkenyl substituted by one or more substituents selected
from the group consisting of:

20

-OH;

-halogen;

-N(R₆)₂;

-CO-N(R₆)₂;

-CS-N(R₆)₂;

25

-SO₂-N(R₆)₂;

-NR₆-CO-C₁₋₁₀ alkyl;

-NR₆-CS-C₁₋₁₀ alkyl;

-NR₆-SO₂-C₁₋₁₀ alkyl;

-CO-C₁₋₁₀ alkyl;

30

-CO-O-C₁₋₁₀ alkyl;

-N₃;

-aryl;

-substituted aryl;
-heteroaryl;
-substituted heteroaryl;
-heterocyclyl;
-substituted heterocyclyl;
-CO-aryl;
-CO-(substituted aryl);
-CO-heteroaryl; and
-CO-(substituted heteroaryl);

R_3 and R_4 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio;

R_5 is H or C_{1-10} alkyl, or R_5 can join with X to form a ring that contains one or two hetero atoms;

each R_6 is independently H or C_{1-10} alkyl;

R_7 is H or C_{1-10} alkyl which may be interrupted by one or more heteroatoms or when R_1 is alkyl, R_7 and R_1 can join to form a ring;
or a pharmaceutically acceptable salt thereof.

Preparation of the Compounds

Compounds of the invention can be prepared according to Reaction Scheme I where R_1 , R_2 , R_3 , R_4 , R_5 , X, Y and Z are as defined above, Bn is benzyl and R' is alkyl of one to four carbon atoms, perfluoroalkyl of one to four carbon atoms, phenyl, or phenyl substituted by halogen or alkyl of one to four carbon atoms.

In step (1) of Reaction Scheme I a 3-nitropyridine-2,4-disulfonate of Formula X is reacted with an amine of Formula $R_1-Z-Y-N(R_5)-X-NH_2$ to provide a 3-nitro-4-aminopyridine-2-sulfonate of Formula XI. Due to the presence of two sulfonate groups that could in principle be displaced, the reaction may provide a mixture of products that can be readily separated using conventional techniques such as column chromatography. The reaction is preferably carried out by adding the amine to a solution of a compound of Formula X in a suitable solvent such as dichloromethane in the presence of a tertiary

amine such as triethylamine. As the sulfonate group is a relatively facile leaving group, the reaction can be run at a reduced temperature (0°C) in order to decrease the amount of undesired 2-aminated and 2,4-diaminated side products. 3-Nitropyridine-2,4-disulfonates are known and can be readily prepared using known synthetic methods, see for example,
5 Lindstom et al., U.S. Patent No. 5,446,153 and the references cited therein.

In step (2) of Reaction Scheme I a 3-nitro-4-aminopyridine-2-sulfonate of Formula XI is reacted with dibenzylamine to provide a 2-dibenzylamino-3-nitropyridin-4-amine of Formula XII. The reaction is carried out by combining a compound of Formula XI, dibenzylamine, and a tertiary amine such as triethylamine in an inert solvent such as
10 benzene, toluene or xylene and heating the resulting mixture.

In step (3) of Reaction Scheme I the nitro group of a 2-dibenzylamino-3-nitropyridin-4-amine of Formula XII is reduced to an amino group. The reduction is preferably carried out using Ni_2B which is generated in situ from sodium borohydride and nickel chloride hydrate in methanol. The reaction is preferably carried out at ambient
15 temperature.

In step (4) of Reaction Scheme I a 2-dibenzylaminopyridine-3,4-diamine of Formula XIII is reacted with a carboxylic acid or an equivalent thereof to provide a 4-dibenzylamino-1*H*-imidazo[4,5-*c*]pyridine of Formula XV. Suitable equivalents to carboxylic acid include orthoesters and 1,1-dialkoxyalkyl alkanoates. The carboxylic acid or equivalent is selected such that it will provide the desired R_2 substituent in a compound of Formula XV. For example, triethyl orthoformate will provide a compound where R_2 is hydrogen and triethyl orthoacetate will provide a compound where R_2 is methyl. The reaction can be run in the absence of solvent or in an inert solvent such as toluene. The reaction is run with sufficient heating to drive off any alcohol or water formed as a
20 byproduct of the reaction. Optionally a catalyst such as pyridine hydrochloride can be included.

Alternatively a compound of Formula XV can be prepared in two steps by (a) reacting a diamine of Formula XIII with an acyl halide of formula $\text{R}_2\text{C}(\text{O})\text{Cl}$ or $\text{R}_2\text{C}(\text{O})\text{Br}$ to provide a compound of Formula XIV and then (b) cyclizing. In step (4a) the acyl halide
30 is added to a solution of the diamine in an inert solvent such as acetonitrile, pyridine or dichloromethane. The reaction can be carried out at ambient temperature. In step (4b) the product of step (4a) is heated in an alcoholic solvent in the presence of a base. Preferably

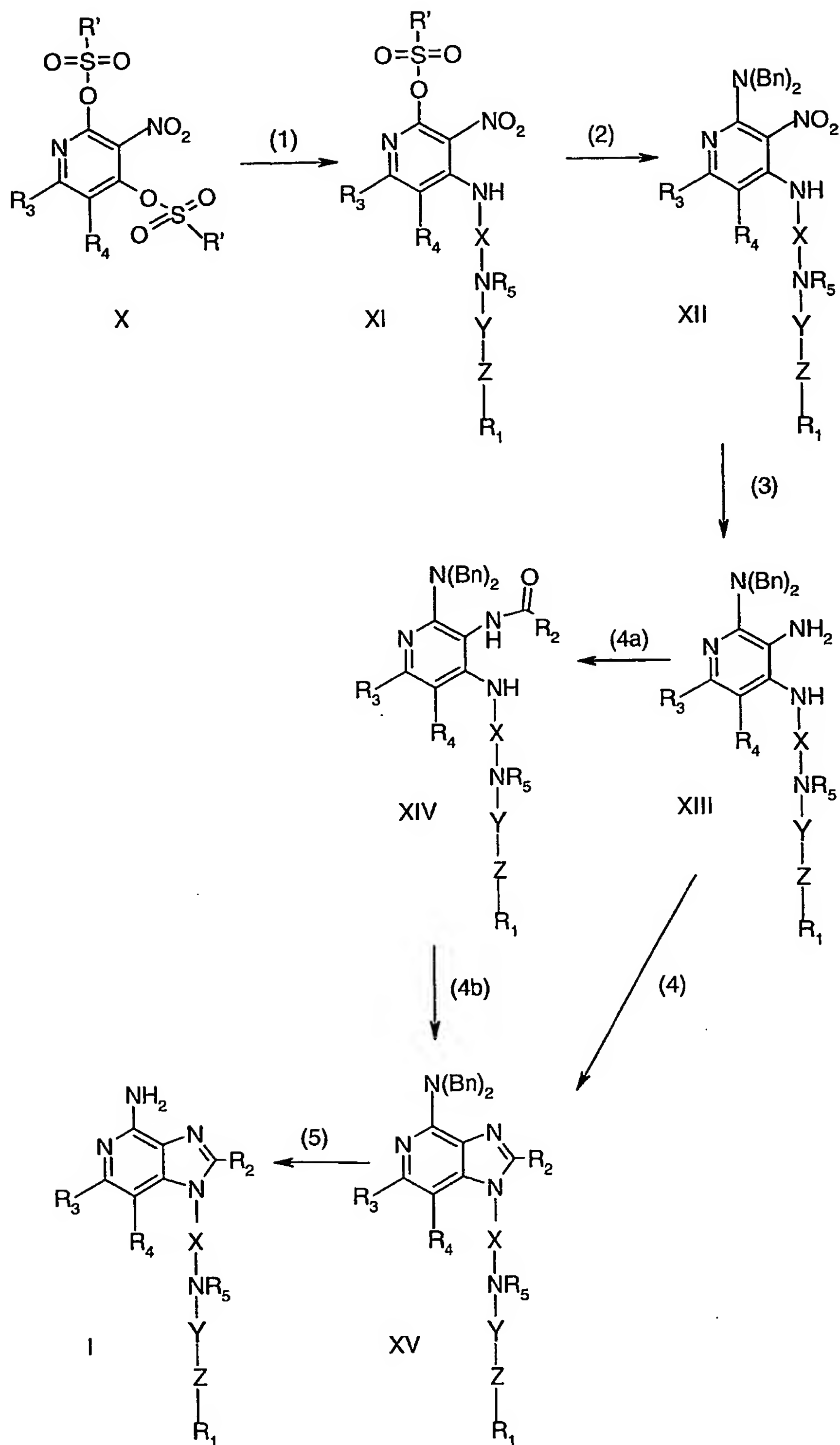
the product of step (4a) is refluxed in ethanol in the presence of an excess of triethylamine or heated with methanolic ammonia. Alternatively step (4b) can be carried out by heating the product of step (4a) in pyridine. If step (4a) was carried out in pyridine, step (4b) can be carried out by heating the reaction mixture after analysis indicates that step (4a) is complete.

5

In step (5) of Reaction Scheme I a 4-dibenzylamino-1*H*-imidazo[4,5-*c*]pyridine of Formula XV is hydrogenolyzed to provide the 4-amino-1*H*-imidazo[4,5-*c*]pyridine of Formula I. Preferably the compound of Formula XV is heated in formic acid in the presence of palladium hydroxide on carbon. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

10

Reaction Scheme I



Compounds of the invention can be prepared according to Reaction Scheme II where R_1 , R_2 , R_3 , R_4 , R_5 and X are as defined above, Bn is benzyl, BOC is *tert*-butoxycarbonyl and W is O or S.

In step (1) of Reaction Scheme II the amine protecting groups of a 1*H*-imidazo[4,5-*c*]pyridine of Formula XVI are removed to provide a 1*H*-imidazo[4,5-*c*]pyridine of Formula II. Preferably a solution of a compound of Formula XVI in a suitable solvent such as dichloromethane is treated with triflic acid at ambient temperature. Compounds of Formula XVI can be prepared using the synthetic method described in Reaction Scheme I. In step (1) a 2,4-disulfonate of Formula X is reacted with an amine of formula BOC-NR₅-X-NH₂. Steps 2-4 are then carried out as described above to provide a compound of Formula XVI which is a subgenus of Formula XV.

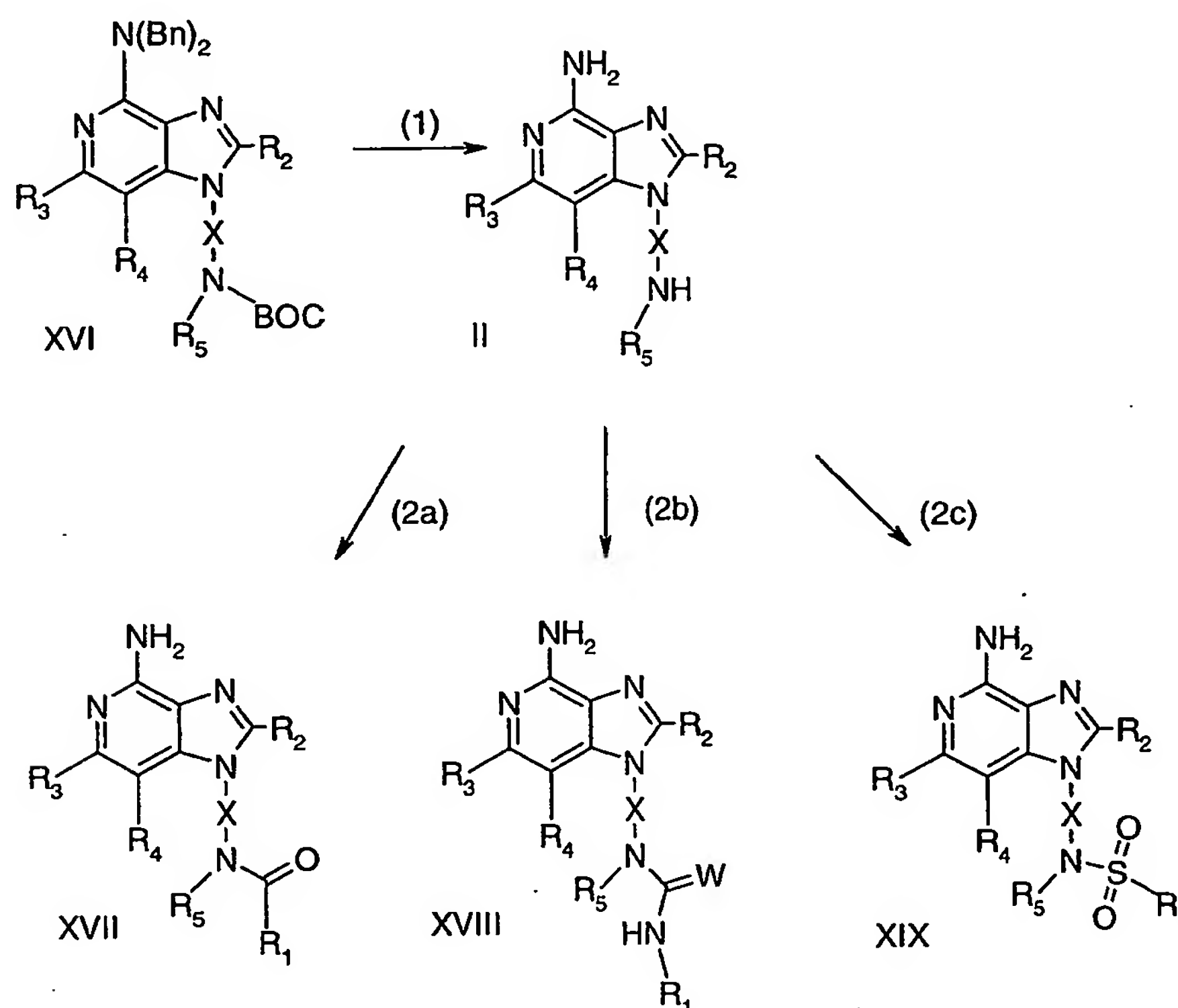
In step (2a) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]pyridine of Formula II is reacted with an acid chloride of formula R₁-C(O)Cl or an acid anhydride of formula R₁-C(O)OC(O)-R₁ to provide a 1*H*-imidazo[4,5-*c*]pyridin-1-yl amide of Formula XVII. The reaction is preferably carried out by adding the acid chloride or acid anhydride to a solution of a compound of Formula II in a suitable solvent such as dichloromethane or acetonitrile in the presence of a base such as triethylamine. The reaction can be run at a reduced temperature (0°C) or at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (2b) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]pyridine of Formula II is reacted with an isocyanate of formula R₁-N=C=O or with an isothiocyanate of formula R₁-N=C=S to provide a 1*H*-imidazo[4,5-*c*]pyridin-1-yl urea or thiourea of Formula XVIII which is a subgenus of Formula I. The reaction is preferably carried out by adding the isocyanate or isothiocyanate to a solution of a compound of Formula II in a suitable solvent such as dichloromethane at a reduced temperature (0°C). The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (2c) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]pyridine of Formula II is reacted with a sulfonyl chloride of formula R₁-S(O)₂Cl or a sulfonic anhydride of formula R₁-S(O)₂OS(O)₂-R₁ to provide a 1*H*-imidazo[4,5-*c*]pyridin-1-yl sulfonamide of Formula XIX. The reaction is preferably carried out by adding the sulfonyl chloride or sulfonic anhydride to a solution of a compound of Formula II in a suitable solvent such as dichloromethane in the presence of a base such as triethylamine. The reaction can be run

at a reduced temperature (0°C) or at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme II



5

Compounds of the invention can be prepared according to Reaction Scheme III where R₁, R₂, R₃, R₄, R₅, R₆ and X, are as defined above.

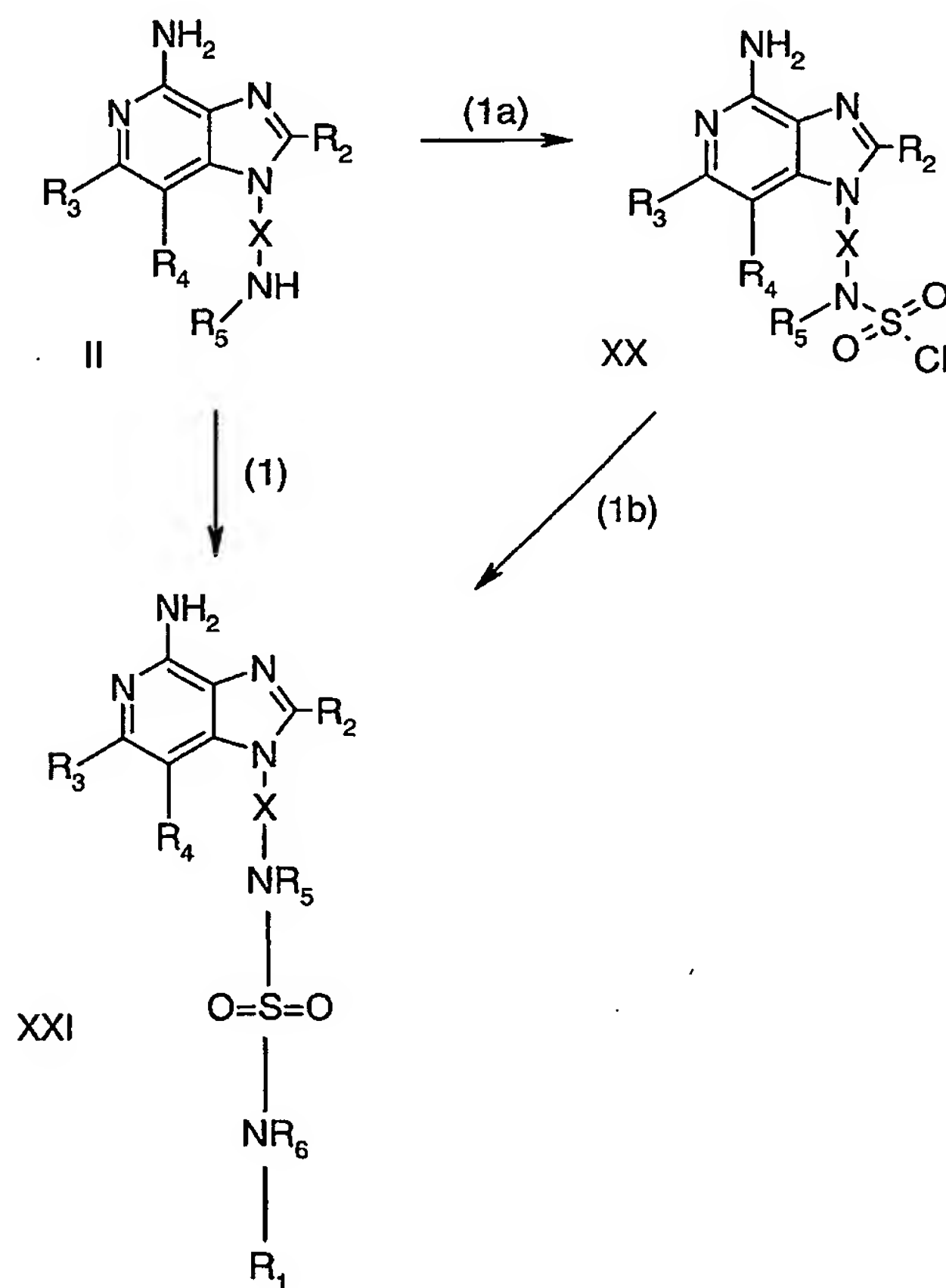
In step (1) of Reaction Scheme III a 1H-imidazo[4,5-c]pyridine of Formula II is reacted with a sulfamoyl chloride of formula R₁-N(R₆)S(O)₂Cl to provide a 1H-imidazo[4,5-c]pyridin-1-yl sulfamide of Formula XXI. Preferably the sulfamoyl chloride is added to a solution of the compound of Formula II in a suitable solvent such as 1,2-dichloroethane in the presence of a base such as triethylamine. The reaction can be run at an elevated temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

15

Alternatively a sulfamide of Formula XXI can be prepared in two steps by (a) reacting a 1H-imidazo[4,5-c]pyridine of Formula II with sulfuryl chloride to generate *in situ* a sulfamoyl chloride of Formula XX and then (b) reacting the sulfamoyl chloride with

an amine of formula $R_1-N(R_6)H$. In step (1a) the reaction can be carried out by adding a solution of sulfonyl chloride in dichloromethane to a solution of a compound of Formula II in the presence of 1 equivalent of 4-(dimethylamino)pyridine. The reaction is preferably carried out at a reduced temperature (-78°C). Optionally, after the addition is complete the reaction mixture can be allowed to warm to ambient temperature. In step (1b) a solution containing 2 equivalents of $R_1-N(R_6)H$ and 2 equivalents of triethylamine in dichloromethane is added to the reaction mixture from step (1a). The reaction is preferably carried out at a reduced temperature (-78°C). The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme III



Compounds of the invention can be prepared according to Reaction Scheme IV where R_1 , R_2 , R_3 , R_4 , R_5 , and X are as defined above and BOC is *tert*-butoxycarbonyl.

In step (1) of Reaction Scheme IV a 2,4-dihydroxy-3-nitropyridine of Formula XXII is chlorinated using conventional chlorinating agents to provide a 2,4-dichloro-3-nitropyridine of Formula XXIII. Preferably a compound of Formula XXII is combined with phosphorous oxychloride and heated. Many 2,4-dihydroxy-3-nitropyridines of Formula XXII are known and others can be readily prepared using known synthetic methods, see for example, Lindstrom et al., U.S. Patent No. 5,446,153 and the references cited therein.

In step (2) of Reaction Scheme IV a 2,4-dichloro-3-nitropyridine of Formula XXIII is reacted with an amine of formula $\text{BOC-NR}_5\text{-X-NH}_2$ to provide a 2-chloro-3-nitropyridine of Formula XXIV. The reaction is preferably carried out by adding the amine to a solution of a compound of Formula XXIII in a suitable solvent such as *N,N*-dimethylformamide in the presence of a tertiary amine such as triethylamine, and optionally heating.

In step (3) of Reaction Scheme IV a 2-chloro-3-nitropyridine of Formula XXIV is reacted with phenol to provide a 3-nitro-2-phenoxy pyridine of Formula XXV. Phenol is reacted with sodium hydride in a suitable solvent such as diglyme or tetrahydrofuran to form the phenoxide. The phenoxide is then reacted at ambient temperature, or optionally at an elevated temperature, with a compound of Formula XXIV.

In step (4) of Reaction Scheme IV a 3-nitro-2-phenoxy pyridine of Formula XXV is reduced to provide a 3-amino-2-phenoxy pyridine of Formula XXVI. Preferably, the reduction is carried out using a conventional heterogeneous hydrogenation catalyst such as platinum on carbon or palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as isopropyl alcohol, toluene or mixtures thereof.

In step (5) of Reaction Scheme IV a 3-amino-2-phenoxy pyridine of Formula XXVI is reacted with a carboxylic acid or an equivalent thereof to provide a 4-phenoxy-1*H*-imidazo[4,5-*c*]pyridine of Formula IV. Suitable equivalents to carboxylic acid include orthoesters, and 1,1-dialkoxyalkyl alkanoates. The carboxylic acid or equivalent is selected such that it will provide the desired R_2 substituent in a compound of Formula IV. For example, triethyl orthoformate will provide a compound where R_2 is hydrogen and

trimethyl orthovalerate will provide a compound where R₂ is butyl. The reaction can be run in the absence of solvent or in an inert solvent such as toluene. The reaction is run with sufficient heating to drive off any alcohol or water formed as a byproduct of the reaction. Optionally a catalyst such as pyridine hydrochloride can be included.

5 Alternatively, step (5) can be carried out by (i) reacting a compound of Formula XXVI with an acyl halide of formula R₂C(O)Cl or R₂C(O)Br and then (ii) cyclizing. In part (i) the acyl halide is added to a solution of a compound of Formula XXV in an inert solvent such as acetonitrile, pyridine or dichloromethane. The reaction can be carried out at ambient temperature. Optionally a catalyst such as pyridine hydrochloride can be included. In part (ii) the product of part (i) is heated in pyridine. If step (i) is run in
10 pyridine, then the two steps can be combined into a single step.

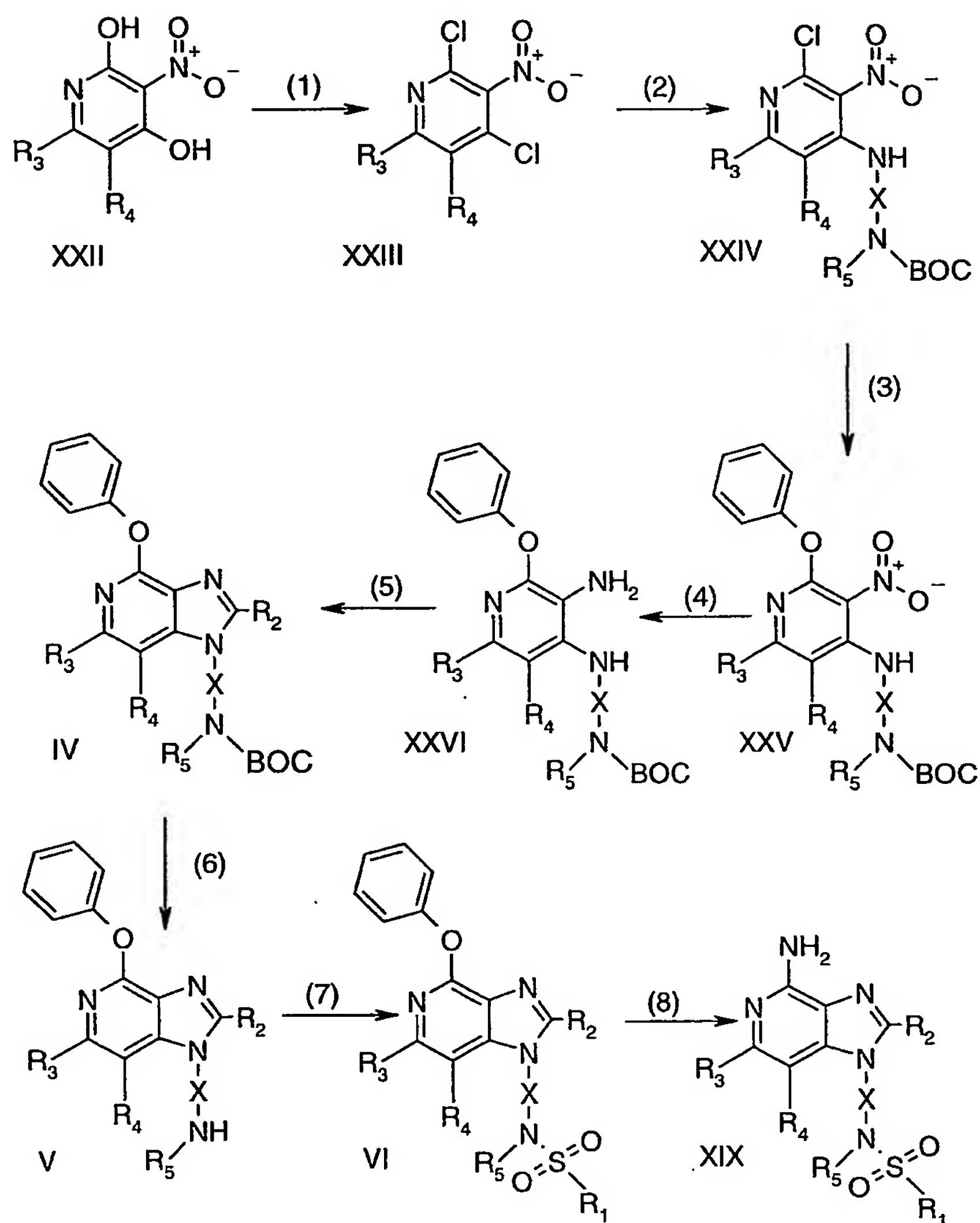
 In step (6) of Reaction Scheme IV the BOC group is removed from a compound of Formula IV to provide 4-phenoxy-1*H*-imidazo[4,5-*c*]pyridine of Formula V. Preferably a solution of a compound of Formula IV in a suitable solvent such as dichloromethane is
15 treated with trifluoroacetic acid or hydrochloric acid at a reduced temperature.

 In step (7) of Reaction Scheme IV a 4-phenoxy-1*H*-imidazo[4,5-*c*]pyridine of Formula V is converted to a 4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl sulfonamide of Formula VI using the method of step (2c) of Reaction Scheme II.

 In step (8) of Reaction Scheme IV 4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl sulfonamide of Formula VI is aminated to provide a 4-amino-1*H*-imidazo[4,5-*c*]pyridin-1-yl sulfonamide of Formula XIX.. The reaction can be carried out by combining a
20 compound of Formula VI with ammonium acetate in a sealed tube and heating (~150°C.). The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

25

Reaction Scheme IV



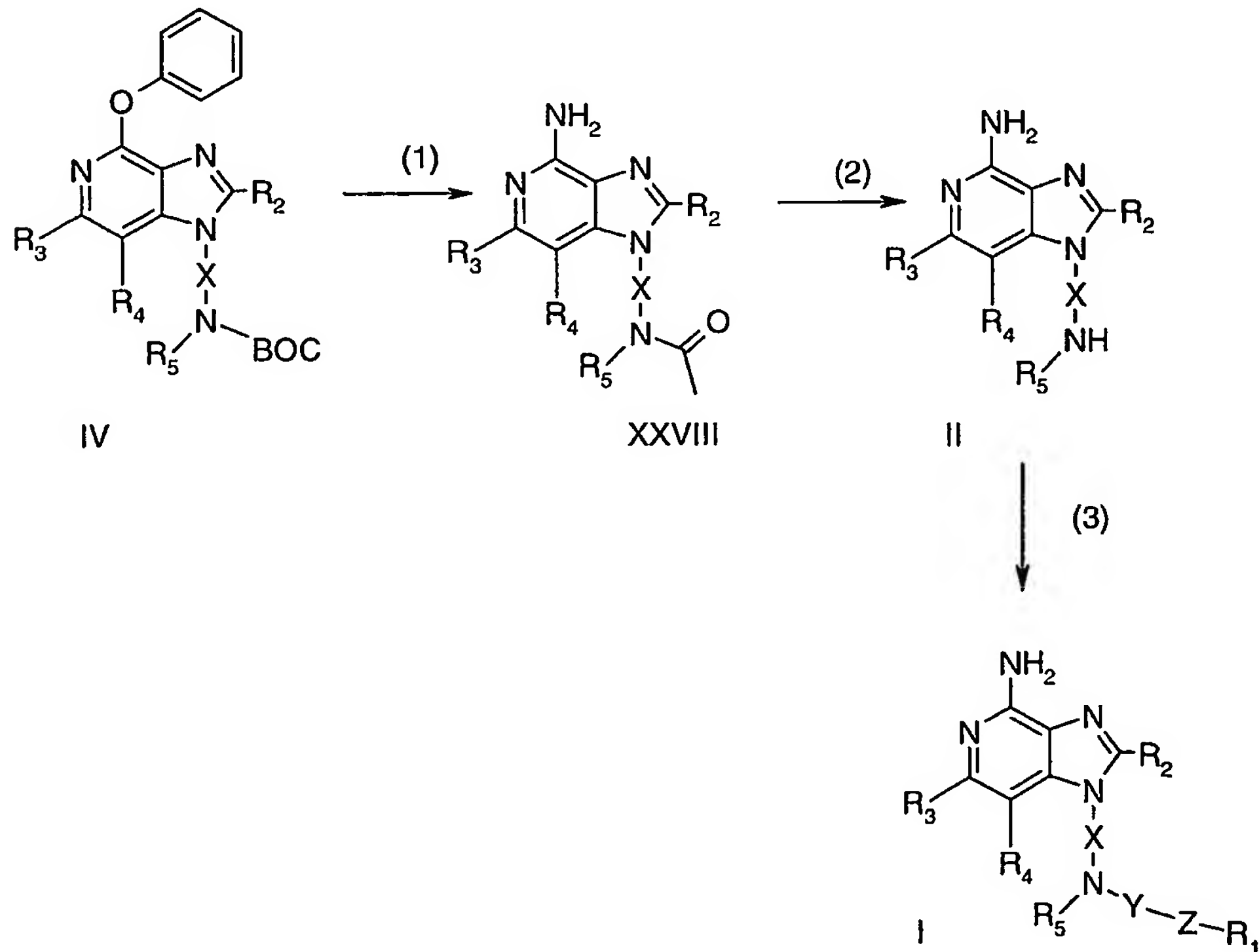
- 5 Compounds of the invention can be prepared according to Reaction Scheme V where R_1 , R_2 , R_3 , R_4 , R_5 , and X are as defined above and BOC is *tert*-butoxycarbonyl.
- 10 In step (1) of Reaction Scheme V, a 4-phenoxy-1*H*-imidazo[4,5-*c*]pyridine of Formula IV is aminated to provide an N-(4-amino-1*H*-imidazo[4,5-*c*]pyridin-1-yl)acetamide of Formula XXVIII, which is a subgenus of Formula I. Preferably a compound of Formula IV is combined with ammonium acetate at an elevated temperature (140 - 160°C). Optionally, the reaction can be run in a pressure vessel.

In step (2) of Reaction Scheme V, an N-(4-amino-1*H*-imidazo[4,5-*c*]pyridin-1-yl)acetamide of Formula XXVIII is hydrolyzed under acidic conditions to provide a 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula II. Preferably, a compound of Formula XXVIII is combined with aqueous hydrochloric acid/ethanol and heated.

5 In step (3) of Reaction Scheme V, a 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula II is converted using conventional methods to a urea or thiourea of Formula I. For example, a compound of Formula II can be reacted with an isocyanate of Formula $R_1N=C=O$. The reaction can be carried out by adding the isocyanate to a solution of a compound of Formula II in a suitable solvent such as chloroform, optionally in the presence of a base such as triethylamine, at ambient temperature. Alternatively, a compound of Formula II can be reacted with a isothiocyanate of Formula $R_1N=C=S$, a sulfonyl isocyanate of Formula $R_1S(O_2)N=C=O$ or a carbamoyl chloride of Formula $R_1R_6NC(O)Cl$. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

15

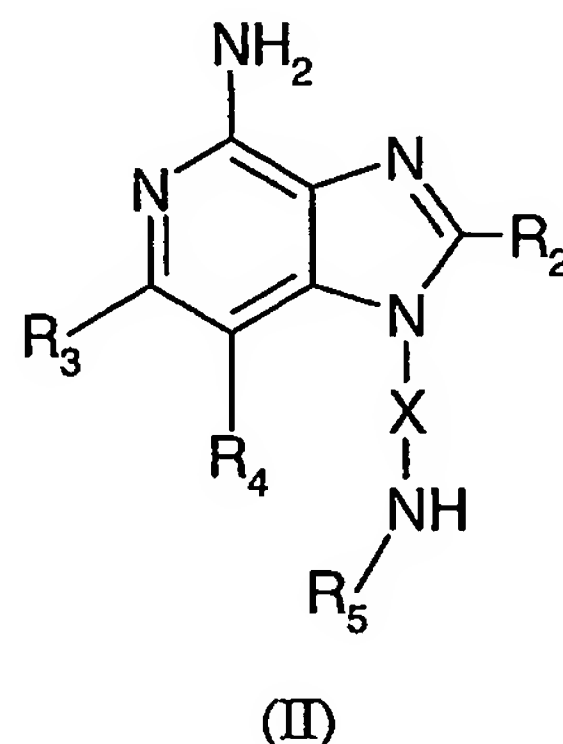
Reaction Scheme V



The invention also provides novel compounds useful as intermediates in the synthesis of the compounds of Formula I. These intermediates have structural Formulas (II) - (VI) described in more detail below.

One class of intermediate compounds has Formula (II):

5



wherein: **X** is alkylene or alkenylene;

10

R₂ is selected from the group consisting of:

15

-hydrogen;

-alkyl;

-alkenyl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

-alkyl-S-aryl;

-alkyl-O- alkenyl;

-alkyl-S- alkenyl; and

20

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-N(R₆)₂;

25

-CO-N(R₆)₂;

-CS-N(R₆)₂;

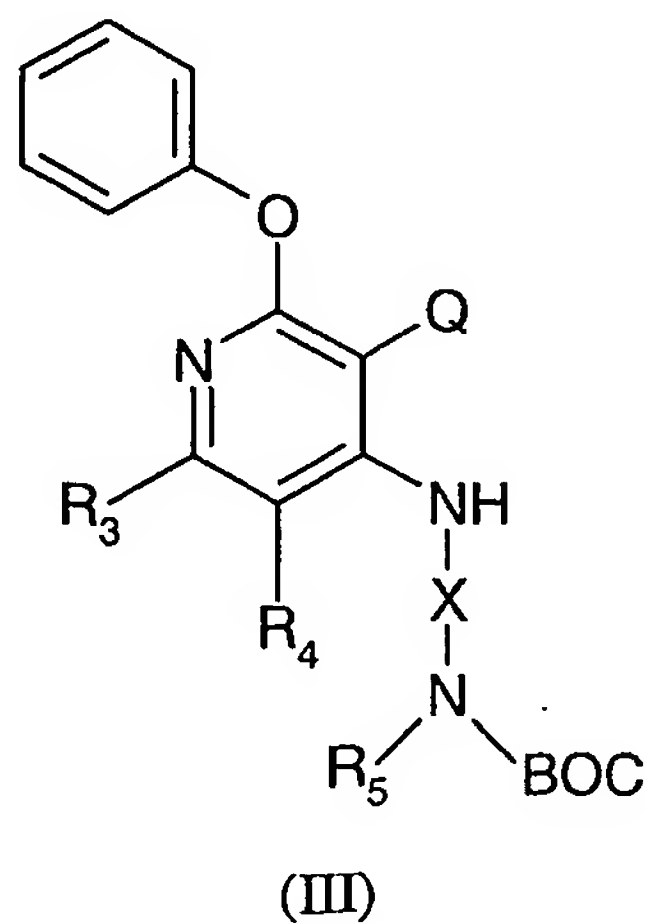
-SO₂-N(R₆)₂;
 -NR₆-CO-C₁₋₁₀ alkyl;
 -NR₆-CS-C₁₋₁₀ alkyl;
 -NR₆-SO₂-C₁₋₁₀ alkyl;
 -CO-C₁₋₁₀ alkyl;
 -CO-O-C₁₋₁₀ alkyl;
 -N₃;
 -aryl;
 -heteroaryl;
 -heterocyclyl;
 -CO-aryl; and
 -CO-heteroaryl;

R₃ and R₄ are independently selected from the group consisting of
 hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and
 alkylthio; and

R₅ is H or C₁₋₁₀ alkyl, or R₅ can join with X to form a ring that contains one
 or two hetero atoms;

each R₆ is independently H or C₁₋₁₀ alkyl;
 or a pharmaceutically acceptable salt thereof.

Another class of intermediates has the Formula III:



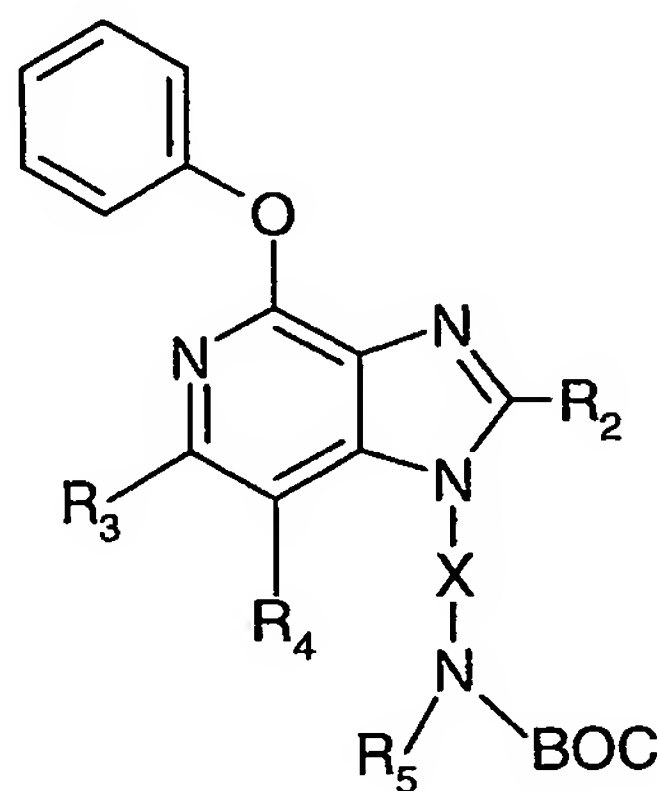
wherein: **Q** is NO₂ or NH₂;

X is alkylene or alkenylene;

R₃ and **R**₄ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio; and

R₅ is H or C₁₋₁₀ alkyl, or **R**₅ can join with **X** to form a ring that contains one or two hetero atoms;
or a pharmaceutically acceptable salt thereof.

Another class of intermediates has the Formula (IV):



(IV)

wherein: **X** is alkylene or alkenylene;

R₂ is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

-alkyl-S-aryl;

-alkyl-O-alkenyl;

-alkyl-S-alkenyl; and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

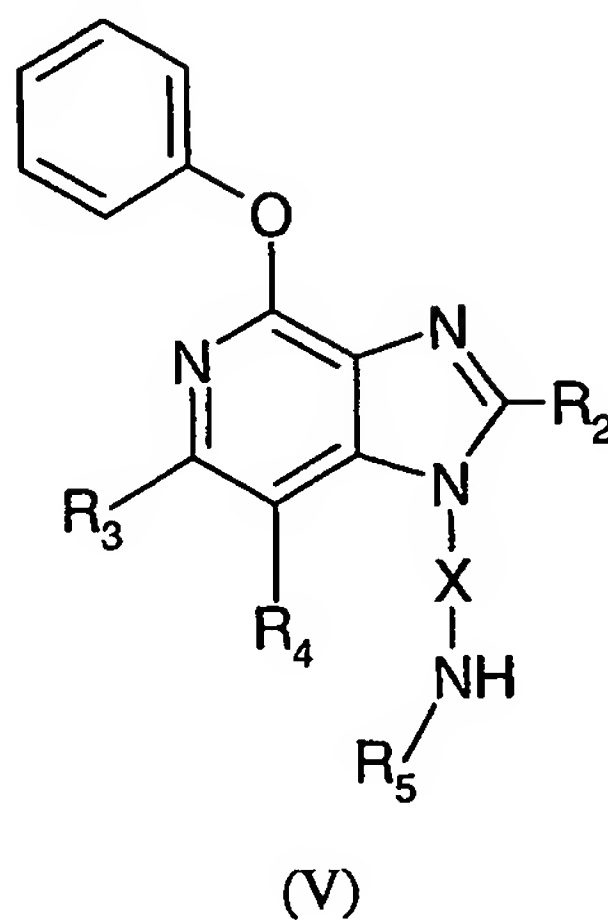
- OH;
- halogen;
- 5 -N(R₆)₂;
- CO-N(R₆)₂;
- CS-N(R₆)₂;
- SO₂-N(R₆)₂;
- NR₆-CO-C₁₋₁₀ alkyl;
- 10 -NR₆-CS-C₁₋₁₀ alkyl;
- NR₆-SO₂-C₁₋₁₀ alkyl;
- CO-C₁₋₁₀ alkyl;
- CO-O-C₁₋₁₀ alkyl;
- N₃;
- 15 -aryl;
- heteroaryl;
- heterocyclyl;
- CO-aryl; and
- CO-heteroaryl;

20 **R**₃ and **R**₄ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio;

R₅ is H or C₁₋₁₀ alkyl, or **R**₅ can join with X to form a ring that contains one or two heteroatoms; and

25 each **R**₆ is independently H or C₁₋₁₀ alkyl;
or a pharmaceutically acceptable salt thereof.

Another class of intermediates has the Formula (V):



5

wherein: X is alkylene or alkenylene;

R₂ is selected from the group consisting of:

10

-hydrogen;

-alkyl;

-alkenyl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

-alkyl-S-aryl;

15

-alkyl-O- alkenyl;

-alkyl-S- alkenyl; and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

20

-halogen;

-N(R₆)₂;

-CO-N(R₆)₂;

-CS-N(R₆)₂;

-SO₂-N(R₆)₂;

25

-NR₆-CO-C₁₋₁₀ alkyl;

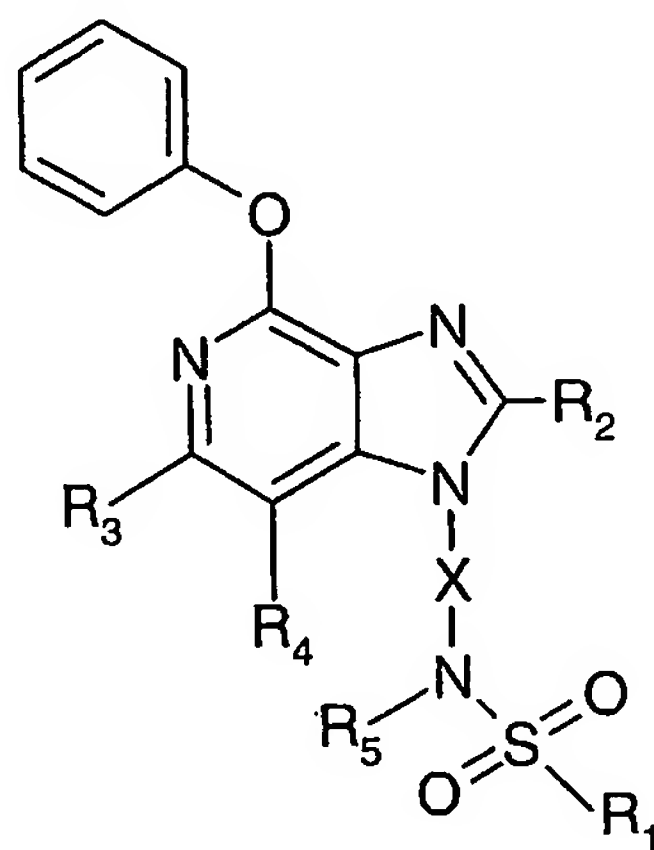
-NR₆-CS-C₁₋₁₀ alkyl;
 -NR₆-SO₂-C₁₋₁₀ alkyl;
 -CO-C₁₋₁₀ alkyl;
 -CO-O-C₁₋₁₀ alkyl;
 -N₃;
 -aryl;
 -heteroaryl;
 -heterocyclyl;
 -CO-aryl; and
 -CO-heteroaryl;

R₃ and **R₄** are independently selected from the group consisting of hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio; and

R₅ is H or C₁₋₁₀ alkyl, or **R₅** and **X** can join to form a ring that contains one or two hetero atoms;

each **R₆** is independently H or C₁₋₁₀ alkyl;
 or a pharmaceutically acceptable salt thereof.

Another class of intermediates has the Formula (VI):



(VI)

wherein: **X** is alkylene or alkenylene;

R_1 is aryl, heteroaryl, heterocyclyl, C_{1-20} alkyl or C_{2-20} alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of:

- alkyl;
- 5 -alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- substituted cycloalkyl;
- 10 -O-alkyl;
- O-(alkyl)₀₋₁-aryl;
- O-(alkyl)₀₋₁-heteroaryl;
- O-(alkyl)₀₋₁-heterocyclyl;
- COOH;
- 15 -CO-O-alkyl;
- CO-alkyl;
- S(O)₀₋₂-alkyl;
- S(O)₀₋₂-(alkyl)₀₋₁-aryl;
- S(O)₀₋₂-(alkyl)₀₋₁-heteroaryl;
- 20 -S(O)₀₋₂-(alkyl)₀₋₁-heterocyclyl;
- (alkyl)₀₋₁-N(R₆)₂;
- (alkyl)₀₋₁-NR₆-CO-O-alkyl;
- (alkyl)₀₋₁-NR₆-CO-alkyl;
- (alkyl)₀₋₁-NR₆-CO-aryl;
- 25 -(alkyl)₀₋₁-NR₆-CO-heteroaryl;
- N₃;
- halogen;
- haloalkyl;
- haloalkoxy;
- 30 -CO-haloalkyl;
- CO-haloalkoxy;
- NO₂;

-CN;

-OH;

-SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R₂ is selected from the group consisting of:

5

-hydrogen;

-alkyl;

-alkenyl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

10

-alkyl-O-aryl;

-alkyl-S-aryl;

-alkyl-O- alkenyl;

-alkyl-S- alkenyl; and

-alkyl or alkenyl substituted by one or more substituents selected

15

from the group consisting of:

-OH;

-halogen;

-N(R₆)₂;

-CO-N(R₆)₂;

20

-CS-N(R₆)₂;

-SO₂-N(R₆)₂;

-NR₆-CO-C₁₋₁₀ alkyl;

-NR₆-CS-C₁₋₁₀ alkyl;

-NR₆- SO₂-C₁₋₁₀ alkyl;

25

-CO-C₁₋₁₀ alkyl;

-CO-O-C₁₋₁₀ alkyl;

-N₃;

-aryl;

-heteroaryl;

30

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

R_3 and R_4 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio; and

R_5 is H or C_{1-10} alkyl, or R_5 and X can join to form a ring that contains one or two hetero atoms;

each R_6 is independently H or C_{1-10} alkyl; or a pharmaceutically acceptable salt thereof.

As used herein, the terms "alkyl", "alkenyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms. Preferred groups have a total of up to 10 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, and adamantyl.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl. The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, and so on.

"Heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, isothiazolidinyl, and imidazolidinyl.

The aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, methylenedioxy, ethylenedioxy, alkylthio, haloalkyl, haloalkoxy, haloalkylthio, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylthio, arylalkoxy, arylalkylthio, heteroaryl, heteroaryloxy, heteroarylthio, heteroarylalkoxy, heteroarylalkylthio, amino, alkylamino, dialkylamino, heterocyclyl, heterocycloalkyl, alkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, haloalkylcarbonyl, haloalkoxycarbonyl, alkylthiocarbonyl, arylcarbonyl, heteroarylcarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylthiocarbonyl, heteroarylthiocarbonyl, alkanoyloxy, alkanoylthio, alkanoylamino, arylcarbonyloxy, arylcarbonythio, alkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryldiazinyl, alkylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, arylcarbonylamino, arylalkylcarbonylamino, heteroarylcarbonylamino, heteroarylalkylcarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, heteroarylsulfonylamino, heteroarylalkylsulfonylamino, alkylaminocarbonylamino, alkenylaminocarbonylamino, arylaminocarbonylamino, arylalkylaminocarbonylamino, heteroarylaminocarbonylamino, heteroarylalkylaminocarbonylamino and, in the case of heterocyclyl, oxo. If other groups are described as being "substituted" or "optionally substituted", then those groups can also be substituted by one or more of the above enumerated substituents.

Certain substituents are generally preferred. For example, Y is preferably $-\text{CO}-$; Z is preferably $-\text{NR}_6-$; and R_1 is preferably C_{1-4} alkyl, aryl, or substituted aryl. Preferred R_2 groups include alkyl groups having 1 to 4 carbon atoms (i.e., methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl), methoxyethyl, ethoxymethyl, and cyclopropylmethyl. R_3 and R_4 are preferably methyl. One or more of these preferred substituents, if present, can be present in the compounds of the invention in any combination.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound of the invention as described above in combination with a pharmaceutically acceptable carrier.

The term "a therapeutically effective amount" means an amount of the compound sufficient to induce a therapeutic effect, such as cytokine induction, antitumor activity, and/or antiviral activity. Although the exact amount of active compound used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg, of the compound to the subject. Any of the conventional dosage forms may be used, such as tablets, lozenges, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

The compounds of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds according to the invention generally include interferon- α (IFN- α) and/or tumor necrosis factor- α (TNF- α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds of the invention include IFN- α , TNF- α , IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds useful in the

treatment of viral diseases and tumors. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or composition of the invention to the animal.

5 Certain compounds of the invention have been found to preferentially induce the expression of IFN- α in a population of hematopoietic cells such as PBMCs (peripheral blood mononuclear cells) containing pDC2 cells (precursor dendritic cell-type 2) without concomitant production of significant levels of inflammatory cytokines.

10 In addition to the ability to induce the production of cytokines, the compounds of the invention affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds may also activate macrophages, which in turn stimulates secretion of nitric oxide and the production of additional cytokines. Further, the compounds may cause proliferation and differentiation of B-lymphocytes.

15 Compounds of the invention also have an effect on the acquired immune response. For example, although there is not believed to be any direct effect on T cells or direct induction of T cell cytokines, the production of the T helper type 1 (Th1) cytokine IFN- γ is induced indirectly and the production of the T helper type 2 (Th2) cytokines IL-4, IL-5 and IL-13 are inhibited upon administration of the compounds. This activity means that the compounds are useful in the treatment of diseases where upregulation of the Th1
20 response and/or downregulation of the Th2 response is desired. In view of the ability of compounds of the invention to inhibit the Th2 immune response, the compounds are expected to be useful in the treatment of atopic diseases, e.g., atopic dermatitis, asthma, allergy, allergic rhinitis; systemic lupus erythematosus; as a vaccine adjuvant; and possibly as a treatment for recurrent fungal diseases and chlamydia.

25 The immune response modifying effects of the compounds make them useful in the treatment of a wide variety of conditions. Because of their ability to induce the production of cytokines such as IFN- α and/or TNF- α , the compounds are particularly useful in the treatment of viral diseases and tumors. This immunomodulating activity suggests that compounds of the invention are useful in treating diseases such as, but not
30 limited to, viral diseases including genital warts; common warts; plantar warts; Hepatitis B; Hepatitis C; Herpes Simplex Virus Type I and Type II; molluscum contagiosum; variola, particularly variola major; HIV; CMV; VZV; rhinovirus; adenovirus; coronavirus;

influenza; and para-influenza; intraepithelial neoplasias such as cervical intraepithelial neoplasia; human papillomavirus (HPV) and associated neoplasias; fungal diseases, e.g. candida, aspergillus, and cryptococcal meningitis; neoplastic diseases, e.g., basal cell carcinoma, hairy cell leukemia, Kaposi's sarcoma, renal cell carcinoma, squamous cell carcinoma, myelogenous leukemia, multiple myeloma, melanoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, and other cancers; parasitic diseases, e.g. pneumocystis carinii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection, and leishmaniasis; and bacterial infections, e.g., tuberculosis, and mycobacterium avium. Additional diseases or conditions that can be treated using the compounds of the invention include actinic keratosis; eczema; eosinophilia; essential thrombocythaemia; leprosy; multiple sclerosis; Ommen's syndrome; discoid lupus; Bowen's disease; Bowenoid papulosis; alopecia areata; the inhibition of Keloid formation after surgery and other types of post-surgical scars. In addition, these compounds could enhance or stimulate the healing of wounds, including chronic wounds. The compounds may be useful for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

An amount of a compound effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN- α , TNF- α , IL-1, IL-6, IL-10 and IL-12 that is increased over the background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μ g/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μ g/kg to about 5 mg/kg. An amount of a compound effective to treat

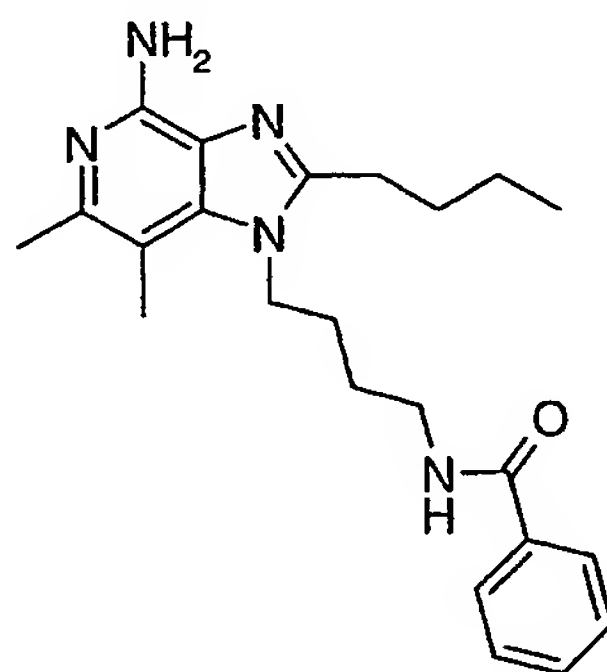
a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg.

5 The invention is further described by the following examples, which are provided for illustration only and are not intended to be limiting in any way.

10 In the examples below some of the compounds were purified by preparative high performance liquid chromatography using a Waters Fraction Lynx automated purification system. The prep HPLC fractions were analyzed using a Micromass LC-TOFMS and the appropriate fractions were combined and centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Column: Phenomenex Luna C18(2), 21.2 x 50 mm, 10 micron particle size, 100Å pore; flow rate: 25 mL/min.; non-linear gradient elution from 5-95% B in 12 min, then hold at 95% B for 2 min., where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile; fraction
15 collection by mass-selective triggering.

Example 1

20 *N*-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]benzamide



Part A

25 Triethylamine (16.8 mL, 123.8 mmol) was added to a suspension of 4-hydroxy-5,6-dimethyl-3-nitro-2(1*H*)-pyridone (7.6 g, 41.2 mmol) in dichloromethane (200 mL).

The resulting mixture was cooled in an ice bath. Triflic anhydride (13.7 mL, 82.5 mmol) was added and the reaction mixture was stirred for 30 minutes. Mono-*tert*-butoxycarbonyl-1,4-butyldiamine (7.6 g, 41.2 mmol) was added in a single portion and the reaction mixture was allowed to warm to ambient temperature. After 1 hour the reaction mixture was washed with aqueous 1% sodium carbonate (2 X 100 mL), dried over magnesium sulfate and then concentrated under reduced pressure to provide crude product. This material was dissolved in dichloromethane and loaded onto a layer of silica gel. The silica gel was eluted first with dichloromethane to remove some impurities and then with 2-5% ethyl acetate in dichloromethane to recover the desired product. The fractions containing product were combined and then concentrated under reduced pressure to provide 12 g of 4-({4-[(*tert*-butoxycarbonyl)amino]butyl}amino)-5,6-dimethyl-3-nitropyridin-2-yl trifluoromethanesulfonate as a light yellow oil.

Part B

The material from Part A was combined with triethylamine (2.5 g, 24.7 mmol), dibenzylamine (4.8 g, 24.7 mmol), and toluene (150 mL) and then heated at reflux for 4 hours. The reaction mixture was washed with aqueous 1% sodium carbonate and then concentrated under reduced pressure to provide crude product. This material was dissolved in dichloromethane and loaded onto silica gel. The silica gel was eluted with 2-20% ethyl acetate in dichloromethane. The fractions containing product were combined and then concentrated under reduced pressure to provide ~13 g of *tert*-butyl 4-{{2-(dibenzylamino)-5,6-dimethyl-3-nitropyridin-4-yl}amino}butylcarbamate.

Part C

Sodium borohydride (1.4 g, 36 mmol) was slowly added to a solution of nickel chloride hydrate (2.9 g, 12.3 mmol) in methanol and the resulting mixture was stirred for 30 minutes. A solution of the material from Part B in methanol was added in a single portion. Sodium borohydride was slowly added until the foaming was colorless. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure. The resulting residue was combined with dichloromethane and the mixture was filtered to remove salts. The filtrate was concentrated under reduced pressure to provide ~12 g of *tert*-butyl 4-{{3-amino-2-(dibenzylamino)-5,6-dimethylpyridin-4-yl}amino}butylcarbamate.

Part D

Valeryl chloride (3 mL, 24.7 mmol) was added to a solution of the material from Part C in acetonitrile (200 mL). The reaction mixture was stirred at ambient temperature. The reaction mixture was concentrated under reduced pressure. The residue was
5 combined with ethanol and triethylamine (5 g, 49 mmol.). The reaction mixture was heated at reflux overnight and then concentrated under reduced pressure. The resulting residue was partitioned between dichloromethane and water. The dichloromethane layer was separated and then loaded onto a silica gel column. The column was eluted with 9:90:1 ethyl acetate:dichloromethane: methanol. The fractions containing product were
10 combined and then concentrated under reduced pressure to provide 6.5 g of *tert*-butyl 4-[2-butyl-4-(dibenzylamino)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butylcarbamate as an oil.

Part E

15 Triflic acid (16g, 107 mmol) was added to a solution of the material from Part D (6.5g, 11.4 mmol) in dichloromethane (250 mL). The resulting mixture was stirred overnight. Ammonium hydroxide (50 mL) and water (100 mL) were added and the resulting mixture was stirred for 30 minutes. The layers were separated and the aqueous fraction was extracted with dichloromethane (100 mL). The organic fractions were
20 combined, washed with 1% aqueous sodium carbonate, washed with brine and concentrated under reduced pressure. The residue was combined with methanol (30 mL), stirred for 30 minutes and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was combined with 1% aqueous sodium carbonate and stirred. The mixture was extracted with hexane to remove organic impurities. The aqueous layer
25 contained an insoluble oil that was extracted with dichloromethane. The organic layer was combined with magnesium sulfate, stirred for 5 minutes and filtered. The filtrate was concentrated under reduced pressure to provide a solid which was recrystallized from toluene to provide 1g of 1-(4-aminobutyl)-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine.

30

Part F

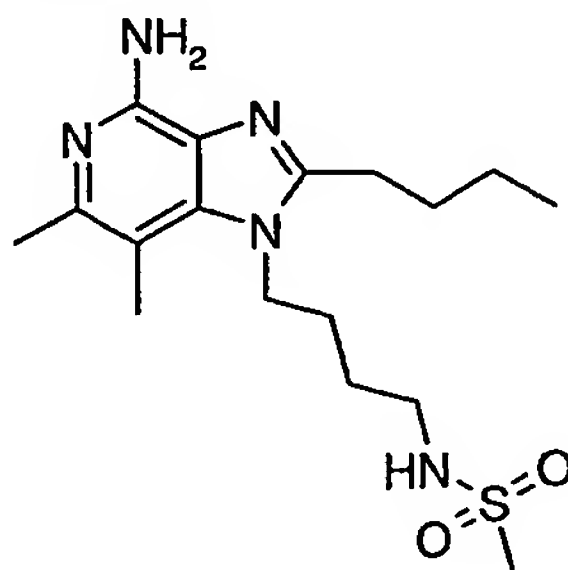
Triethylamine (0.07 mL, 0.5 mmol) was added to a solution of 1-(4-aminobutyl)-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (150 mg, 0.5 mmol) in dichloromethane (150 mL). The reaction mixture was cooled in an ice bath. Benzoyl chloride (0.07 mL, 0.5 mmol) was added and the reaction mixture was removed from the ice bath. The reaction mixture was washed twice with water and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography eluting with 10% methanol in dichloromethane to provide an oily brown material. This material was dissolved in a minimum amount of isopropanol and then ethanesulfonic acid (55 mg, 0.5 mmol) was added with stirring. The reaction mixture was stirred at ambient temperature for ~1 hour and then heated briefly in a sand bath until it became homogeneous. The solution was allowed to cool to ambient temperature and then was chilled in an ice bath. The resulting precipitate was isolated by filtration to provide 111 mg of *N*-[4-(4-amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]benzamide as a crystalline solid, m.p. 127.8-128.8°C.

Analysis: Calculated for C₂₃H₃₁N₅O: %C, 70.20; %H, 7.94; %N, 17.80; Found: %C, 69.82; %H, 7.70; %N, 17.68.

20

Example 2

N-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]methanesulfonamide



25

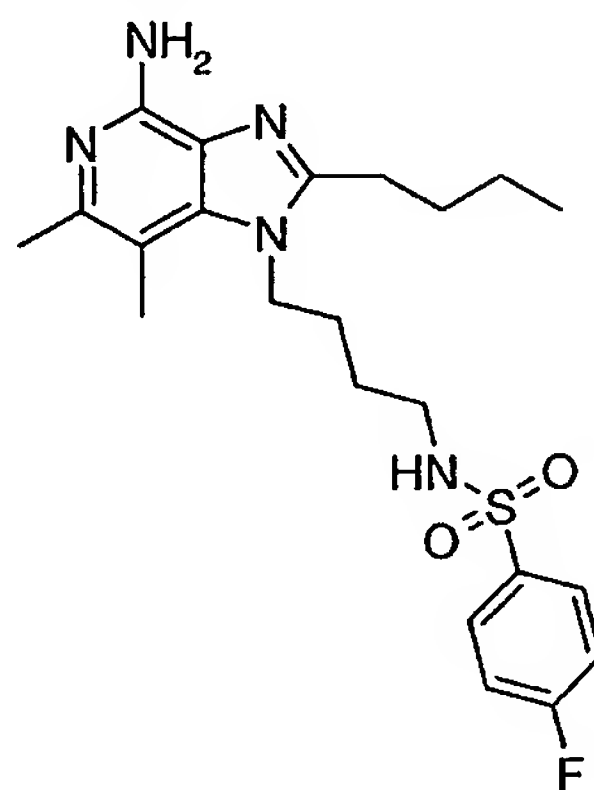
Triethylamine (0.07 mL, 0.5 mmol) was added to a solution of 1-(4-aminobutyl)-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (150 mg, 0.5 mmol) in dichloromethane (160 mL). The reaction mixture was cooled in an ice bath.

Methanesulfonic anhydride (90 mg, 0.5 mmol) was added and the reaction mixture was removed from the ice bath. The reaction mixture was stirred for 35 minutes. The reaction mixture was washed three times with water, concentrated under reduced pressure, and triturated with a minimum volume of methyl acetate. The resulting crystalline solid was isolated by filtration and then dried in an Abderhalden drying apparatus to provide 94 mg of *N*-[4-(4-amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]methanesulfonamide, m.p. 130-130.5°C

Analysis: Calculated for C₁₇H₂₉N₅O₂S: %C, 55.56; %H, 7.95; %N, 19.06; Found: %C, 55.37; %H, 7.89; %N, 18.03.

Example 3

N-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-4-fluorobenzenesulfonamide Hydrate



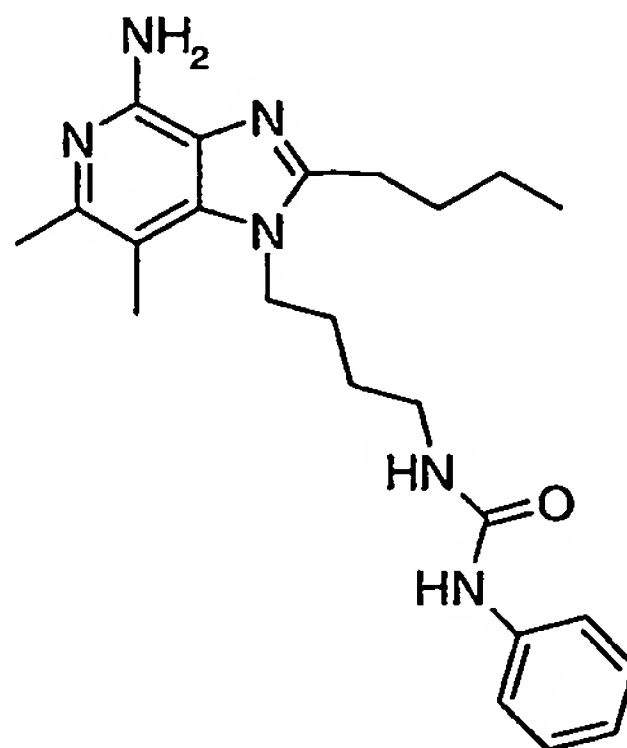
Triethylamine (0.07 mL, 0.5 mmol) was added to a solution of 1-(4-aminobutyl)-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (150 mg, 0.5 mmol) in dichloromethane (150 mL). The reaction mixture was cooled in an ice bath. 4-Fluorobenzenesulfonyl chloride (113 mg, 0.5 mmol) was added and the reaction mixture was removed from the ice bath. The reaction mixture was stirred at ambient temperature for 48 hours. The reaction mixture was washed with water (2 X 150 mL) and then concentrated under reduced pressure. The resulting residue was recrystallized from methyl acetate and then dried in an Abderhalden drying apparatus to provide 50 mg of *N*-

[4-(4-amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-4-fluorobenzenesulfonamide hydrate as a white crystalline solid, m.p. 133.1-133.7°C. Analysis: Calculated for $C_{22}H_{30}FN_5O_2S \cdot H_2O$: %C, 56.75; %H, 6.93; %N, 15.04; Found: %C, 56.99; %H, 6.58; %N, 15.24.

5

Example 4

N-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-*N'*-phenylurea



10

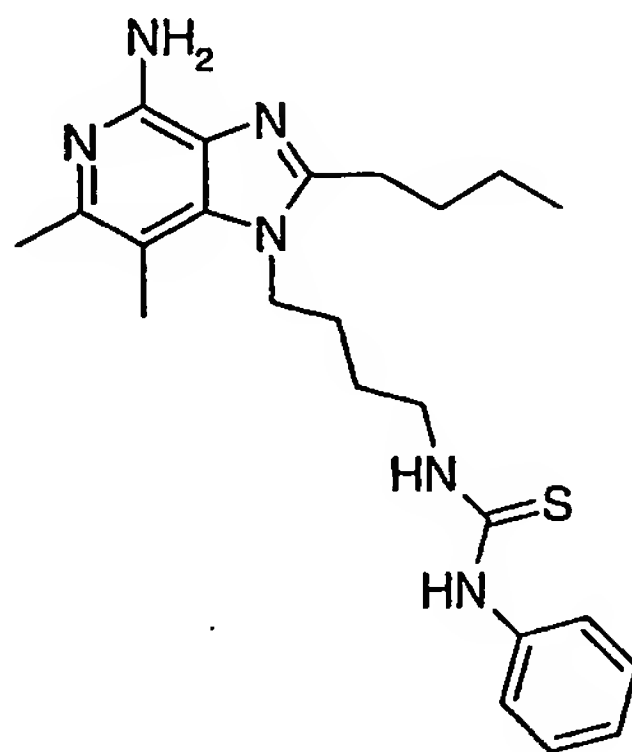
Phenylisocyanate (0.056 mL, 0.5 mmol) was added to a chilled solution of 1-(4-aminobutyl)-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (150 mg, 0.5 mmol) in dichloromethane (150 mL). The ice bath was removed. A white precipitate formed after 5 minutes. The reaction mixture was allowed to stir for 30 minutes and then it was concentrated under reduced pressure to provide an off-white crystalline solid. This material was isolated by filtration using a small amount of diethyl ether to transfer the material to the filter and then dried in an Abderhalden drying apparatus to provide 185 mg of *N*-[4-(4-amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-*N'*-phenylurea, m.p. 195.8-196.8°C.

Analysis: Calculated for $C_{23}H_{32}N_6O$: %C, 67.62; %H, 7.89; %N, 20.57; Found: %C, 66.84; %H, 7.71; %N, 20.54.

20

Example 5

N-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-*N'*-phenylthiourea Hydrate



5

Using the method of Example 4, 1-(4-aminobutyl)-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (100 mg, 0.35 mmol) was reacted with phenylisothiocyanate (0.041 mL, 0.35 mmol) to provide 97 mg of *N*-[4-(4-amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-*N'*-phenylthiourea hydrate as a white crystalline solid, m.p. 160.0-160.8°C.

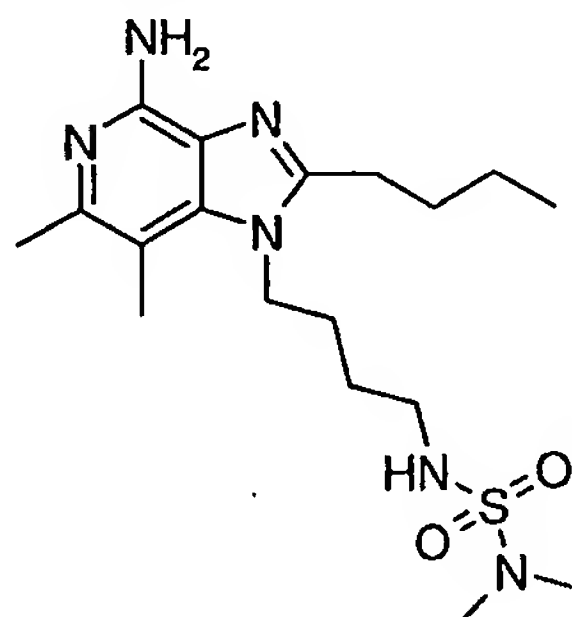
10

Analysis: Calculated for $C_{23}H_{32}N_6S \cdot H_2O$: %C, 62.41; %H, 7.74; %N, 18.99; Found: %C, 62.39; %H, 7.47; %N, 18.52.

15

Example 6

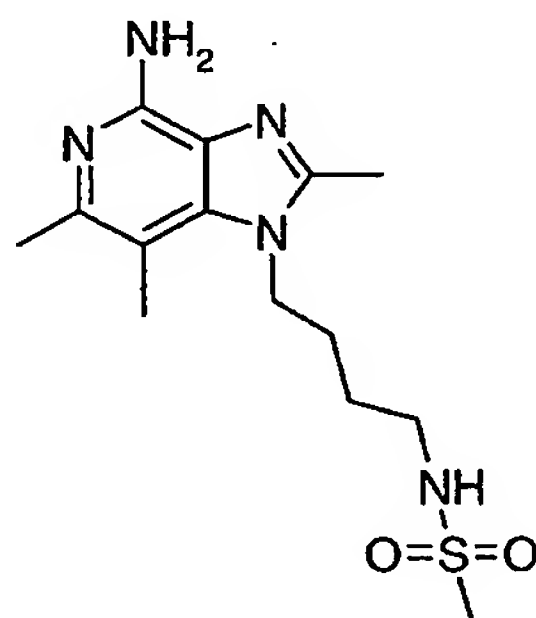
N-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-*N,N*-dimethylsulfamide



Triethylamine (0.031 mL, 0.23 mmol) was added to a solution of 1-(4-aminobutyl)-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (67 mg, 0.23 mmol) in dichloromethane (45 mL). The reaction mixture was cooled in an ice bath. Dimethylsulfamoyl chloride (0.025 mL, 0.23 mmol) was added. The reaction mixture was removed from the ice bath. The reaction mixture was allowed to stir at ambient temperature for ~113 hours. Analysis by HPLC indicated that the reaction was not complete. The dichloromethane was removed under reduced pressure. 1,2-Dichloroethane (50 mL) was added and the reaction mixture was heated to 60°C. After 3 hours, more dimethylsulfamoyl chloride (2.5 μ L) was added and heating was continued. After 22 hours the reaction temperature was raised to reflux and the reaction mixture was refluxed for 100 hours. The reaction mixture was extracted twice with water. The aqueous fractions were combined and concentrated under reduced pressure. The resulting residue was recrystallized from methyl acetate to provide 10 mg of *N*-[4-(4-amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-*N,N*-dimethylsulfamide as an off-white crystalline solid, m.p. 129.5-131°C. $M/Z = 397.1$ ($M + H$)⁺.

Example 7

N-[4-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]methanesulfonamide



Part A

A mixture of 5,6-dimethyl-3-nitropyridine-2,4-diol (60.0 g, 326 mmol) and phosphorus oxychloride (600 mL) was heated at reflux for 2 hrs. The reaction mixture was concentrated under reduced pressure. The resulting residue was combined with ethyl

acetate (300 mL) and then filtered. The filtrate was washed with aqueous sodium bicarbonate solution. The layers were separated and aqueous layer was extracted twice with ethyl acetate. The organic layers were combined, dried with magnesium sulfate and then concentrated under reduced pressure to provide a brown solid. This material was
5 purified by chromatography (silica gel eluting with 60/40 ethyl acetate/hexanes) to provide 55 g of 2,4-dichloro-5,6-dimethyl-3-nitropyridine.

Part B

Tert-butyl 4-aminobutylcarbamate (60 g, 339 mmol) was slowly added to a mixture of 2,4-dichloro-5,6-dimethyl-3-nitropyridine (50 g, 226 mmol), anhydrous N,N-dimethylformamide (500 mL) and triethylamine (50 mL, 339 mmol). The reaction
10 mixture was allowed to stir overnight and then it was concentrated under reduced pressure to provide an oil. The oil was dissolved in ethyl acetate and then washed with water. The organic layer was dried over magnesium sulfate and then concentrated under reduced pressure to provide a dark oil. This material was purified by column chromatography
15 (silica gel eluting with 40/60 ethyl acetate/hexanes) to provide 64.5 g of *tert*-butyl 4-(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)butylcarbamate as a bright orange oil which solidified on standing.

Part C

A solution of phenol (18.50 g, 196 mmol) in diglyme (50 mL) was slowly added dropwise to a chilled (0°C) suspension of sodium hydride (8.28 g of 60% in mineral oil, 207 mmol) in diglyme (50 mL). After 1 hr gas evolution ceased. A solution of *tert*-butyl 4-(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)butylcarbamate (68.95 g, 185 mmol) in diglyme (200 mL) was slowly added dropwise to the reaction mixture. After the addition was complete the reaction mixture was heated at reflux for 4 hrs. The reaction mixture
25 was concentrated under reduced pressure to provide a black oil. The oil was dissolved in ethyl acetate and then extracted with 1N sodium hydroxide to remove excess phenol. The organic layer was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by chromatography (silica gel eluting with 30/70 ethyl acetate/hexanes) to provide 40.67 g of *tert*-butyl 4-[(2,3-dimethyl-5-nitro-6-phenoxy-
30 pyridin-4-yl)amino]butylcarbamate as an orange oil.

Part D

Tert-butyl 4-[(2,3-dimethyl-5-nitro-6-phenoxy-pyridin-4-yl)amino]butylcarbamate (9.17 g, 21.3 mmol), toluene (50 mL), isopropanol (5 mL) and 5% platinum on carbon (7.0 g) were combined and maintained under hydrogen pressure (50 psi, 3.5 Kg/cm²) overnight on a Parr apparatus. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting brown oil was dried under high vacuum to provide 7.47 g of *tert*-butyl 4-[(3-amino-5,6-dimethyl-2-phenoxy-pyridin-4-yl)amino]butylcarbamate.

Part E

A mixture of the material from Part D, triethyl orthoacetate (3.59 mL, 19.58 mmol), anhydrous toluene (75 mL) and pyridine hydrochloride (0.75 g) was heated at reflux for 1 hour and then concentrated under reduced pressure to provide a brown oil. The oil was dissolved in ethyl acetate and then washed with water (X2), washed with brine, dried over magnesium sulfate and then concentrated under reduced pressure to provide 6.74 g of *tert*-butyl 4-(2,6,7-trimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butylcarbamate as a brown oil.

Part F

A solution of *tert*-butyl 4-(2,6,7-trimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butylcarbamate (6.70 g, 15.8 mmol) in dichloromethane (50 mL) was slowly added to a chilled (0°C) mixture of trifluoroacetic acid (60 mL) and dichloromethane (100 mL). The reaction mixture was allowed to warm to ambient temperature and then left overnight. The reaction mixture was concentrated under reduced pressure to provide a brown oil. The oil was dissolved in dichloromethane and the solution was made basic (pH 14) with 5% aqueous sodium hydroxide. The layers were separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over magnesium sulfate and then concentrated under reduced pressure to provide 4.50 g of 4-(2,6,7-trimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butylamine as a brown oil.

Part G

A mixture of the material from Part F, triethylamine (2.0 mL, 14.6 mmol) and anhydrous acetonitrile (450 mL) was heated until a homogeneous solution was obtained. Methanesulfonic anhydride (2.54 g, 14.6 mmol) was slowly added to the reaction mixture. The reaction was judged to be complete in 10 minutes. The reaction mixture was

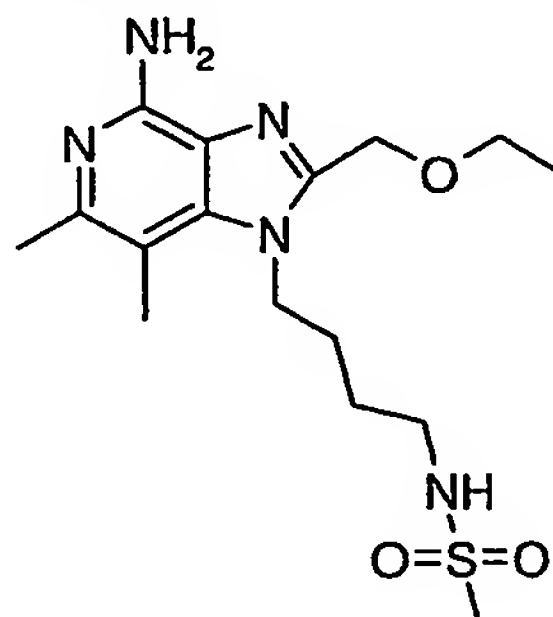
concentrated under reduced pressure to provide a brown oil. The oil was dissolved in dichloromethane and was washed with 5% aqueous sodium hydroxide. The aqueous layer was separated and then extracted with dichloromethane. The organic layers were combined, dried over magnesium sulfate and then concentrated under reduced pressure to provide a brown solid. This material was purified by column chromatography (silica gel eluting with 95/5 dichloromethane/methanol) to provide 4.49 g of *N*-[4-(2,6,7-trimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]methanesulfonamide as a light brown solid.

Part H

N-[4-(2,6,7-trimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]methanesulfonamide (4.20 g, 10.4 mmol) and ammonium acetate (42 g) were combined and then heated in a sealed tube at 150°C for 36 hrs. The reaction mixture was allowed to cool and then it was dissolved in chloroform. The solution was extracted with 10 % aqueous sodium hydroxide solution. The aqueous layer was separated and then extracted multiple times with chloroform. The organic layers were combined, dried over magnesium sulfate and then concentrated under reduced pressure to provide a yellow oil. The oil was dissolved in methanol and combined with 1M hydrochloric acid in diethyl ether (10.4 mL). The resulting white precipitate was isolated by filtration and dried. The solid was dissolved in water and the solution was adjusted to pH 10 with solid sodium carbonate. The resulting white precipitate was isolated by filtration, washed with diethyl ether and then dried in a vacuum oven at 80°C to provide 2.00 g of *N*-[4-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]methanesulfonamide, m.p. 228-230°C. Analysis: Calculated for C₁₄H₂₃N₅O₂S: %C, 51.67; %H, 7.12; %N, 21.52; Found: %C, 51.48; %H, 6.95; %N, 21.51.

Example 8

N-{4-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}methanesulfonamide



5

Part A

Triethylamine (3.3 mL, 23.7 mmol) was added to a chilled (0°C) mixture of *tert*-butyl 4-[(3-amino-5,6-dimethyl-2-phenoxy-4-yl)amino]butylcarbamate (8.60 g, 21.5 mmol) and anhydrous dichloromethane (200 mL). Ethoxyacetyl chloride (2.76 g, 22.5 mmol) was added. After one hour the reaction mixture was allowed to warm to ambient temperature and stirred for 2 hours. The reaction mixture was concentrated under reduced pressure to provide *tert*-butyl 4-({3-[(ethoxyacetyl)amino]-5,6-dimethyl-2-phenoxy-4-yl}amino)butylcarbamate as a brown oil. The oil was combined with pyridine (130 mL) and heated at reflux overnight. The reaction mixture was concentrated under reduced pressure to provide a brown oil. The oil was dissolved in dichloromethane and was washed with water. The organic layer was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was dissolved in diethyl ether and then concentrated under reduced pressure to provide 8.21 g of *tert*-butyl 4-[2-(ethoxymethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butylcarbamate.

20 Part B

Using the method of Part F of Example 7, the material from Part A was hydrolyzed to provide 5.76 g of 4-[2-(ethoxymethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butan-1-amine as a brown oil.

Part C

25 Using the method of Part G of Example 7, 4-[2-(ethoxymethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butan-1-amine (5.52 g, 15.0 mmol) was reacted

with methanesulfonic anhydride (2.74 g, 15.7 mmol) to provide 6.26 g of *N*-{4-[2-(ethoxymethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}methanesulfonamide as a brown solid.

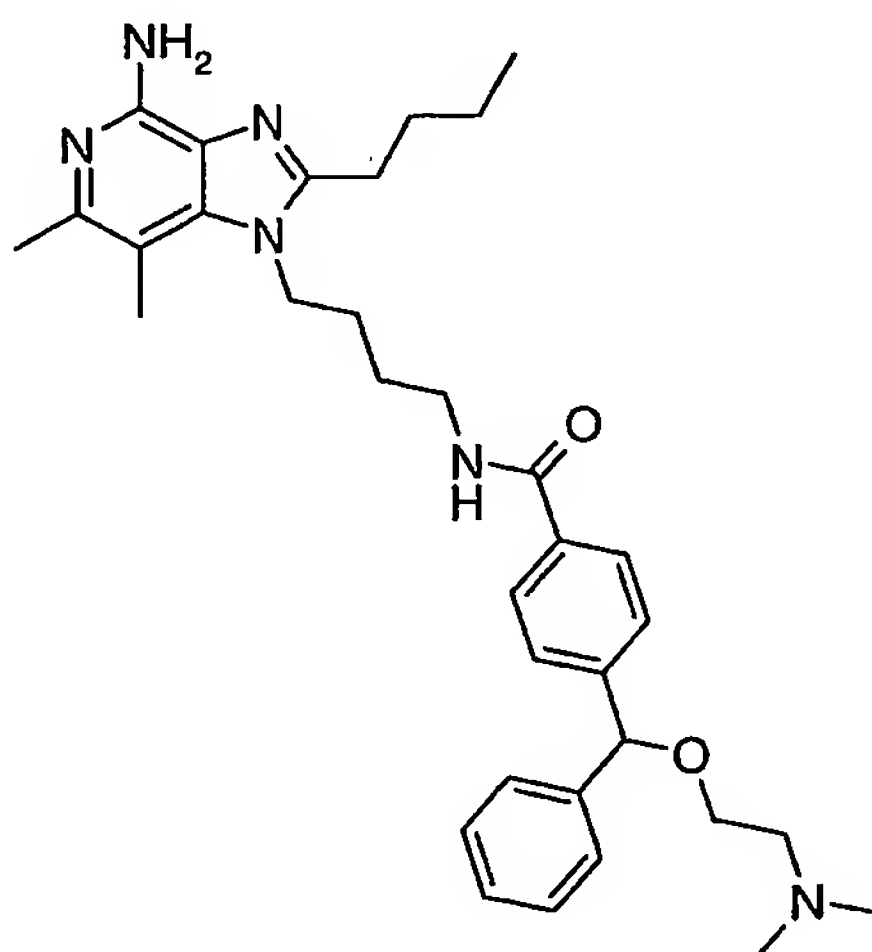
Part D

5 Using the general method of Part H of Example 7, *N*-{4-[2-(ethoxymethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}methanesulfonamide (5.86 g, 13.1 mmol) was aminated to provide 1.58 g of *N*-{4-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}methanesulfonamide as a white solid, m.p. 165-167°C.

10 Analysis: Calculated for C₁₆H₂₇N₅O₃S: %C, 52.01; %H, 7.37; %N, 18.95; Found: %C, 51.83; %H, 7.39; %N, 18.88.

Example 9

15 *N*-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-4-[[2-(dimethylamino)ethoxy](phenyl)methyl]benzamide



20 Part A

Under a nitrogen atmosphere, 4-(2-butyl-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butan-1-amine (122 mg, 0.33 mmol) was dissolved in dichloromethane and triethylamine (0.093 mL, 0.67 mmol). The solution was cooled in an ice-water bath and 4-
25 [[2-(dimethylamino)ethoxy](phenyl)methyl]benzoyl chloride (106 mg, 0.33 mmol) was

dissolved/slurried in dichloromethane and added dropwise. The ice bath was removed and the reaction was stirred for an additional 16 hours. The reaction was quenched with 10% aqueous sodium carbonate. The phases were separated and the aqueous fraction was extracted with dichloromethane. The organic fractions were combined, washed with water followed by brine, dried (Na₂SO₄), decanted and evaporated to yield a yellow oil.

Purification by flash column chromatography (silica gel, 92:8 dichloromethane/methanol gradient to 95:5 dichloromethane/methanol) provided 101 mg of N-[4-(2-butyl-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-4-[[2-(dimethylamino)ethoxy](phenyl)methyl]benzamide as a pale yellow solid. The product was determined to be 97+% pure by HPLC.

MS(CI): 648 (M+H).

Part B

N-[4-(2-Butyl-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-4-[[2-(dimethylamino)ethoxy](phenyl)methyl]benzamide (101 mg, 0.16 mmol) and ammonium acetate (1.1 g) were placed into a pressure tube along with a stir bar. The tube was sealed and heated at 150°C for 16 hours. The reaction was cooled to room temperature and diluted with water. The resulting cloudy aqueous mixture was made basic with 10% aqueous sodium hydroxide and extracted with chloroform (3 x 25mL). The combined organic fractions were washed with water followed by brine, dried (Na₂SO₄), decanted and evaporated to provide a yellow oil. Purification by flash column chromatography (silica gel, 95:5 dichloromethane/methanol gradient to 9:1 dichloromethane/methanol and finally 94:5:1 dichloromethane/methanol/triethylamine) provided 14 mg of N-[4-(4-amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-4-[[2-(dimethylamino)ethoxy](phenyl)methyl]benzamide as a yellow oil.

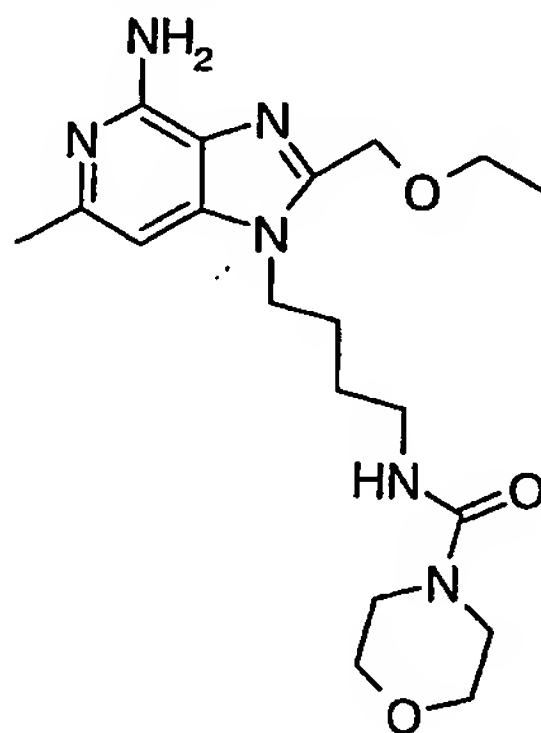
¹H-NMR (500 MHz, DMSO-*d*₆) δ 8.41 (t, *J* = 5.5 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 2H); 7.43 (d, *J* = 8.3, 2H), 7.37-7.31 (m, 4H), 7.26-7.22 (m, 1H), 5.84 (bs, 2H), 5.52 (s, 1H), 4.22 (t, *J* = 7.7 Hz, 2H), 3.49 (t, *J* = 5.8 Hz, 2H), 3.29 (dd, *J* = 6.4, 12.4 Hz, 2H), 2.76 (t, *J* = 7.7 Hz, 2H), 2.58 (t, *J* = 5.7 Hz, 2H), 2.32 (s, 3H), 2.27 (s, 3H), 2.22 (s, 6H), 1.73-1.65 (m, 4H), 1.61-1.55 (m, 2H), 1.35 (sextet, *J* = 7.4 Hz, 2H), 0.86 (t, *J* = 7.4 Hz, 3H);

¹³C-NMR (125 MHz, DMSO-*d*₆) δ 165.9, 153.0, 148.1, 145.4, 142.0, 138.6, 133.5, 128.23, 127.4, 127.3, 127.1, 126.4, 126.1, 124.5, 103.0, 82.0, 66.3, 58.0, 45.2, 43.6, 38.4, 29.3, 28.8, 26.1, 26.0, 21.7, 21.0, 13.6, 12.2.

HRMS (CI) m/e 571.3763 (M+H), (571.3761 calcd for C₃₄H₄₇N₆O₂, M+H).

Example 10

5 N-{4-[4-amino-2-(ethoxymethyl)-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}morpholin-4-ylcarboxamide



Part A

10 A mixture of 6-methyl-3-nitropyridine-2,4-diol (50 g, 0.29 mol) and phosphorus oxychloride (500 mL) was heated at 90°C overnight. The excess phosphorus oxychloride was removed under reduced pressure. The resulting black oil was poured into water (1.8 L) and ice. This mixture was extracted with chloroform (x 8, 3L total) and filtered to remove black particulates and break up an emulsion. The combined organics were washed
15 with 10% sodium carbonate (x 2) and brine, dried and then concentrated under reduced pressure to provide 52 g of an amber oil. This oil was recrystallized from heptane (115 mL) to provide 43.5 g of 2,4-dichloro-6-methyl-3-nitropyridine as large amber crystals.

Part B

20 A solution of *tert*-butyl 4-aminobutylcarbamate (32.12 g, 170.6 mmol) in N,N-dimethylformamide (200 mL) was added over a period of 90 minutes to a solution of 2,4-dichloro-6-methyl-3-nitropyridine (35.09 g, 169.5 mmol) in N,N-dimethylformamide (500 mL). The reaction mixture was stirred at ambient temperature overnight. The solvent was removed by vacuum distillation using a 24/40 short path distillation head and warm water. The residue was dissolved in ethyl acetate (700 mL), washed with water (3 x 100 mL),
25 dried over magnesium sulfate and then concentrated under reduced pressure. The crude

product was purified by column chromatography (50 X 450 mm silica gel eluting with 1:1 hexane:ethyl acetate) to provide 59.90 g of *tert*-butyl 4-[(2-chloro-6-methyl-3-nitropyridin-4-yl)amino]butylcarbamate.

Part C

5 Phenol (9.45 g, 100 mmol) was added over a period of 10 minutes to a chilled (0°C) suspension of sodium hydride (4.24 g of 60%, 106 mmol) in anhydrous tetrahydrofuran (100 mL). The reaction mixture was allowed to stir at 0°C for 30 minutes. A solution of *tert*-butyl 4-[(2-chloro-6-methyl-3-nitropyridin-4-yl)amino]butylcarbamate (33.92 g, 94.5 mmol) in anhydrous tetrahydrofuran (250 mL) was added over a period of
10 50 minutes while maintaining the reaction mixture at 0°C. The reaction mixture was allowed to warm to ambient temperature and stirred overnight before being concentrated under reduced pressure. The residue was dissolved in ethyl acetate (500 mL), washed with 1N sodium hydroxide (300 mL), dried over magnesium sulfate and then concentrated to dryness. The crude product was purified by column chromatography (400 g silica gel
15 eluting with 7:3 hexanes:ethyl acetate to provide 25.4 g of *tert*-butyl 4-[(6-methyl-3-nitro-2-phenoxy-pyridin-4-yl)amino]butylcarbamate.

Part D

 A solution of the material from Part C in a mixture of toluene (300 mL) and isopropanol (33 mL) was combined with catalyst (16.68 g of 5% Pt/C) and placed under
20 hydrogen pressure (30 psi, 2.1 Kg/cm²; recharging once) on a Parr apparatus for 5 hours. The reaction mixture was filtered to remove the catalyst and then concentrated under reduced pressure to provide 23.4 g of *tert*-butyl 4-[(3-amino-6-methyl-2-phenoxy-pyridin-4-yl)amino]butylcarbamate as a dark oil.

Part E

25 The material from Part D was dissolved in dichloromethane (500 mL) and then cooled under a nitrogen atmosphere to 0°C. A solution of ethoxyacetyl chloride (7.9 g, 63.5 mmol) in dichloromethane (200 mL) was added over a period of 40 minutes while maintaining the reaction mixture at 0°C. The reaction mixture was allowed to warm to ambient temperature and was stirred overnight. The reaction mixture was washed with
30 water (2 x 100 mL) and brine (100 mL), dried over magnesium sulfate and then concentrated under reduced pressure to provide 26.4 g of *tert*-butyl 4-[(3-[(ethoxyacetyl)amino]-6-methyl-2-phenoxy-pyridin-4-yl)amino]butylcarbamate.

Part F

The material from Part E was combined with pyridine (250 mL) and pyridine hydrochloride (20.85 g, 180 mmol) and heated at reflux under a nitrogen atmosphere overnight. The bulk of the pyridine was removed by vacuum distillation. The residue was partitioned between ethyl acetate (600 mL) and water (300 mL). The layers were separated. The organic layer was washed with water (2 x 300 mL), dried over magnesium sulfate and then concentrated under reduced pressure to provide 8.17 g of *tert*-butyl 4-[2-(ethoxymethyl)-6-methyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butylcarbamate as a dark oil. The pH of the aqueous layer was adjusted to 11 with 15% sodium hydroxide and then it was extracted with ethyl acetate (5 x 250 mL). The extracts were combined, dried over magnesium sulfate and then concentrated under reduced pressure to provide 9.46 g of 4-[2-(ethoxymethyl)-6-methyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butan-1-amine.

Part G

Benzyl chloroformate (2.2 mL) was added over a period of 2 minutes to a solution of 4-[2-(ethoxymethyl)-6-methyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butan-1-amine (4.96 g, 14 mmol) and triethylamine (2.6 mL) in chloroform (100 mL). The reaction mixture was allowed to stir at ambient temperature for 2.5 hours; it was washed with 1N sodium hydroxide (50 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (208 g silica gel eluting with 2% methanol in chloroform) to provide two fractions (2.2 g and 3.12 g) of benzyl 4-[2-(ethoxymethyl)-6-methyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butylcarbamate.

Part H

The first fraction (2.2 g) from Part G and ammonium acetate (20.3 g) were combined in a pressure vessel (75 mL). The vessel was sealed and then heated at 150°C for 21.5 hours. The reaction mixture was diluted with chloroform (200 mL) and washed with 10% sodium hydroxide (3 x 70 mL). The aqueous layer was extracted with chloroform (6 x 100 mL). The combined organic layers were dried over magnesium sulfate and then concentrated under reduced pressure. Analysis by LCMS indicated that the crude product was a 50/50 mixture of *N*-(4-[4-amino-2-(ethoxymethyl)-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl)acetamide / benzyl 4-[4-amino-2-(ethoxymethyl)-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butylcarbamate.

Part I

A solution of the material from Part H in ethanol (28 mL) was combined with concentrated hydrochloric acid (18.3 mL) in a pressure vessel (150 mL). The vessel was sealed and then heated at 90°C for 21 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in water (100 mL) and then washed with chloroform (3 x 50 mL). The aqueous layer was adjusted to pH >11, saturated with sodium chloride and then extracted with chloroform (8 x 100 mL). The extracts were combined, dried over magnesium sulfate and then concentrated under reduced pressure. The crude product was combined with crude product from another run and then was purified by column chromatography (25 g of silica gel eluting sequentially with 2% methanol in dichloromethane with 0.5% triethylamine (1 L); 4% methanol in chloroform (800 mL); and 6% methanol in chloroform (800 mL) to provide 1.3 g of 1-(4-aminobutyl)-2-ethoxymethyl-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine as a solid, m.p. 108-111°C. Analysis: Calculated for C₁₄H₂₃N₅O • 0.05 HCl: %C, 60.23; %H, 8.32; %N, 25.08; Found: %C, 59.92; %H, 8.26; %N, 24.81.

Part J

4-Morpholinecarbonyl chloride (202 µL, 1.73 mmol) was added to a solution of 1-(4-aminobutyl)-2-ethoxymethyl-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (0.435, 1.57 mmol) in a mixture of triethylamine (280 µL, 2.04 mmol) and chloroform (8 mL). The reaction mixture was stirred at ambient temperature for 4 hours then it was diluted with chloroform (20 mL) and washed with saturated sodium bicarbonate (10 mL). The organic layer was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by column chromatography (30 g of silica gel eluting with 1 L of 2% methanol in chloroform containing 0.5% triethylamine. The resulting glassy solid was triturated with acetonitrile to provide 0.417 g of N-{4-[4-amino-2-(ethoxymethyl)-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}morpholine-4-carboxamide as an off white powder, m.p. 156.5-159.5°C.

Analysis: C₁₉H₃₀N₆O₃ • 0.20 HCl: %C, 57.37; %H, 7.65; %Cl, 1.78; %N, 21.13; Found: %C, 57.19; %H, 7.56; %Cl, 1.84; %N, 21.14.

¹H NMR (300 MHz, CDCl₃) δ 6.51 (s, 1 H), 5.46 (bs, 2 H), 4.71 (s, 2 H), 4.45 (bs, 1 H), 4.17 (t, J = 7.5 Hz, 2 H), 3.68 (t, J = 4.9 Hz, 4 H), 3.57 (quartet, J = 7.1 Hz, 2 H), 3.32 (m,

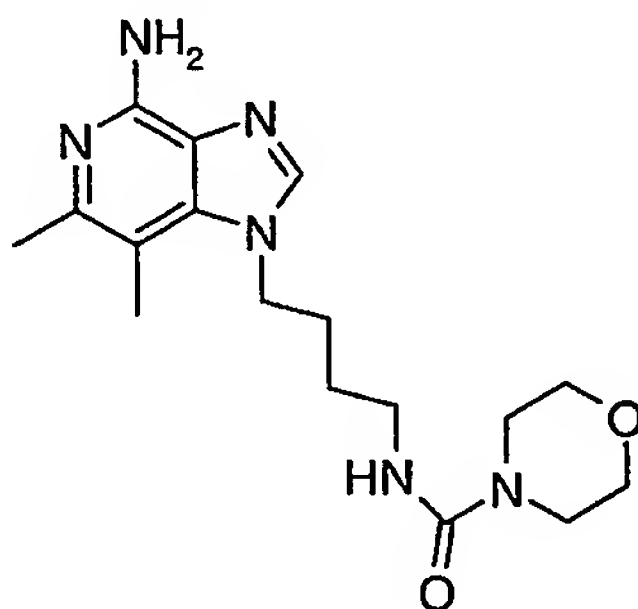
6 H),), 2.49 (s, 3 H), 1.86 (quintet, $J = 7.5$ Hz, 2 H), 1.58 (quintet, $J = 7.3$ Hz, 2 H), 1.22 (t, $J = 7.2$ Hz, 3 H);

MS(CI) m/e 391 (M+H)

5

Example 11

N-[4-(4-amino-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]morpholin-4-ylcarboxamide



10 Part A

A suspension of 5,6-dimethyl-3-nitropyridine-2,4-diol (14.87 g) in phosphorous oxychloride (150 mL) was heated at reflux for 2 hours. Excess phosphorous oxychloride was removed by distillation. The residue was dissolved in water, neutralized with ammonium hydroxide, and extracted twice with ethyl acetate. The organics were combined, washed with brine, dried over sodium sulfate and then concentrated under reduced pressure. The residue was slurried with boiling hexane and then filtered while hot. The filtrate was chilled. The resulting precipitate was isolated by filtration and air dried to provide 6.8 g of 2,4-dichloro-5,6-dimethyl-3-nitropyridine as a white powder.

Part B

20 A solution of *tert*-butyl 4-aminobutylcarbamate (8.52 g, 45.24 mmol) in N,N-dimethylformamide was added to a solution of 2,4-dichloro-5,6-dimethyl-3-nitropyridine (10.00 g, 45.24 mmol) and triethylamine (12.6 mL, 90.5 mmol) in N,N-dimethylformamide (320 mL). The reaction mixture was stirred overnight and then concentrated under reduced pressure. The residue was partitioned between water and ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The organics were combined, washed with brine and then concentrated under reduced pressure to provide a brown oily residue. This material was purified by flash

25

chromatography (400 mL silica gel, eluting initially with 10% ethyl acetate in hexane and then increasing the gradient to 15% and then to 25%) to provide 8.1 g of *tert*-butyl 4-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]butylcarbamate as a yellow solid.

Part C

5 Phenol (2.164 g, 23.00 mmol) was added as a solid over a period of 10 minutes to a suspension of sodium hydride (0.972 g, 24.3 mmol) in diglyme (24 mL). The reaction mixture was allowed to stir for 30 minutes then the material from Part B was added as a solid. The reaction mixture was stirred at 80°C for 2.5 days and then allowed to cool to ambient temperature overnight. The diglyme was removed under reduced pressure to
10 provide an oily residue. The residue was combined with cold water and allowed to stir overnight. Ethyl acetate was added and the layers were separated. The aqueous layer was extracted with ethyl acetate. The organics were combined, washed with water and brine, dried over sodium sulfate and then concentrated under reduced pressure to provide a black oil. This material was purified by flash chromatography (400 mL silica gel eluting with
15 25% ethyl acetate in hexanes) to provide 7.1 g of *tert*-butyl 4-[(2,3-dimethyl-5-nitro-6-phenoxy)pyridin-4-yl]amino]butylcarbamate as an orange oil which later solidified.

Part D

 A solution of *tert*-butyl 4-[(2,3-dimethyl-5-nitro-6-phenoxy)pyridin-4-yl]amino]butylcarbamate (7.32 g, 17.00 mmol) in a mixture of toluene (150 mL) and
20 isopropanol (10 mL) was combined with a slurry of 10% palladium on carbon in toluene. The mixture was placed under hydrogen pressure on a Parr apparatus for 24 hours. Additional catalyst was added at 1.5 hours (2.2 g) and 3 hours (3 g). The reaction mixture was filtered through a layer of Celite® filter agent to remove the catalyst. The layer of filter agent was washed with ethanol (1 L), ethanol/methanol (1 L), and methanol (1 L).
25 The filtrate was concentrated under reduced pressure. The residue was combined with dichloromethane and heptane and then concentrated under reduced pressure to provide 6.17 g of *tert*-butyl 4-[(3-amino-5,6-dimethyl-2-phenoxy)pyridin-4-yl]amino]butylcarbamate as a sludgy brown yellow oil.

Part E

30 Diethoxymethyl acetate (2.76 mL, 16.93 mmol) and pyridine hydrochloride (0.037 g, 0.323 mmol) were added to a solution of the material from Part D in toluene (72 mL). The reaction mixture was heated at reflux for 2 hours and then allowed to cool to ambient

temperature overnight. The reaction mixture was concentrated under reduced pressure and then the residue was twice combined with toluene and concentrated. The resulting oil was dissolved in chloroform; washed with saturated sodium bicarbonate, water and brine; dried over magnesium sulfate and then concentrated under reduced pressure to provide 5.37 g of
5 *tert*-butyl 4-(6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butylcarbamate as a very thick brown oil/solid.

Part F

The material from Part E was combined with ammonium acetate (47 g) in a tube. The tube was sealed and heated at 150°C for 20 hours. The reaction mixture was poured
10 into water and adjusted to pH 10 with 10% sodium hydroxide. The basic solution was extracted with chloroform (x 9). The basic layer was treated with solid sodium chloride and then extracted with chloroform. The organics were combined, dried over sodium sulfate and then concentrated under reduced pressure to provide a yellowish solid. The solid was dissolved in a mixture of chloroform and methanol and then combined with 50
15 mL of 1N hydrochloric acid in diethyl ether. The solvents were removed and the resulting oil was dissolved in water. This solution was extracted with dichloromethane (x 3), made basic (pH 10) with 50% sodium hydroxide, and then extracted with chloroform (x 3). Sodium chloride was added to the aqueous solution and it was extracted with chloroform (x 3). The organics were combined, dried over sodium sulfate and concentrated under
20 reduced pressure to provide a yellow solid. This solid was recrystallized from ethanol to provide 2.62 g of a solid. A portion (500 mg) was dissolved in methanol, concentrated under reduced pressure and then dried in a vacuum oven at 70°C over the weekend to provide 0.46 g of *N*-[4-(4-amino-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]acetamide as a solid, m.p. 217-219°C.

25 Analysis: Calculated for C₁₄H₂₁N₅O: %C, 61.07; %H, 7.69; %N, 25.43; Found: %C, 60.87; %H, 7.75; %N, 25.43.

Part G

A solution of *N*-[4-(4-amino-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]acetamide (~2.1 g) in 6 N hydrochloric acid (30 mL) was sealed in a flask and
30 then heated at 100°C for about 30 hours. The reaction mixture was allowed to cool to ambient temperature and then filtered to remove any particulates. The filtrate was made basic (pH 14) with 25% sodium hydroxide and then extracted with chloroform (x 2). The

aqueous layer was combined with sodium chloride (20 g) and then extracted with chloroform (x 3). The organics were combined, washed with brine, dried over sodium sulfate and then concentrated under reduced pressure to provide 1.44 g of 1-(4-aminobutyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine.

5 Part H

4-Morpholinecarbonyl chloride (0.250 mL, 2.14 mmol) was added drop wise to a slurry of 1-(4-aminobutyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (0.500 g, 2.14 mmol) in chloroform (10 mL). After 1 hour, analysis by high performance liquid chromatography showed about 60% completion. 4-Morpholinecarbonyl chloride (0.200 mL) was added and the reaction mixture was stirred overnight. The reaction mixture was poured into 5% sodium hydroxide and stirred for 10 minutes. The layers were separated. The aqueous layer was extracted with chloroform (x 2). The combined organics were washed with water and brine then dried over magnesium sulfate and concentrated under reduced pressure to provide a yellow oil. The aqueous layer was saturated with sodium chloride and then extracted with dichloromethane (x 3). The extracts were combined, dried and then combined with the yellow oil and concentrated under reduced pressure. The residue was purified by column chromatography (43 g of silica gel eluting with 2% methanol in dichloromethane containing 1% triethylamine and then with 5% methanol in dichloromethane containing 1% triethylamine). The residue was dissolved in dichloromethane and the solution was diluted with hexanes. The resulting precipitate was isolated by filtration and then recrystallized twice from acetonitrile to provide 0.283 g of N-[4-(4-amino-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]morpholine-4-carboxamide as a pale yellow powder, m.p. 163.7-167.0°C.

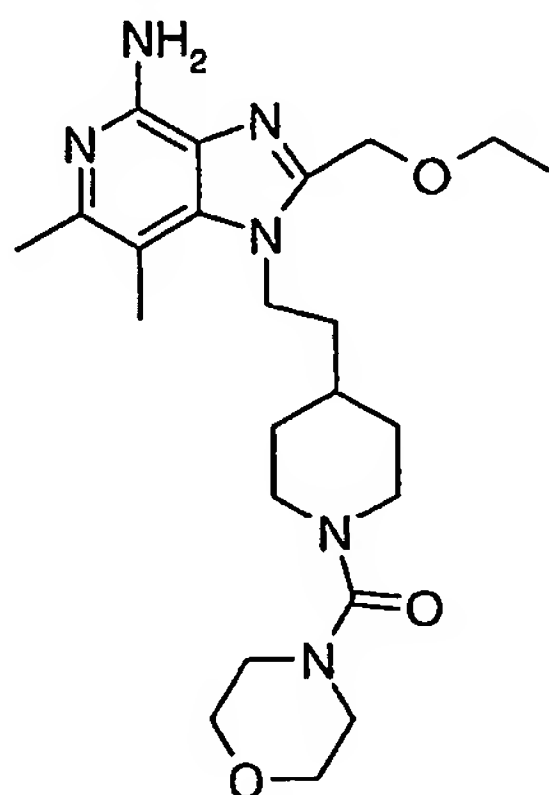
Analysis: Calculated for C₁₇H₂₆N₆O₂: %C, 58.94; %H, 7.56; %N, 24.26; Found: %C, 58.66; %H, 7.69; %N, 24.22.

¹H NMR (300 MHz, DMSO-*d*₆) δ 7.91 (s, 1 H), 6.51 (t, *J* = 5.5 Hz, 1 H), 5.73 (s, 2 H), 4.29 (t, *J* = 7.1 Hz, 2 H), 3.51 (t, *J* = 4.8 Hz, 4 H), 3.20 (t, *J* = 4.8 Hz, 4 H), 3.04 (q, *J* = 6.8 Hz, 2 H), 2.36 (s, 3 H), 2.30 (s, 3 H), 1.70 (quintet, *J* = 7.4 Hz, 2 H), 1.35 (quintet, *J* = 7.4 Hz, 2 H);

MS (CI) *m/e* 347.2197 (347.2195 calcd for C₁₇H₂₆N₆O₂, M+H).

Example 12

2-(ethoxymethyl)-6,7-dimethyl-1-{2-[1-(morpholin-4-ylcarbonyl)piperidin-4-yl]ethyl}-
1*H*-imidazo[4,5-*c*]pyridin-4-amine



5

Part A

A solution of 4-(2-aminoethyl)-1-benzylpiperidine (9.88 g, 45.2 mmol) in *N,N*-dimethylformamide was added dropwise to a solution of 2,4-dichloro-5,6-dimethyl-3-nitropyridine (10.00 g, 45.2 mmol) and triethylamine (12.6 mL, 90.5 mmol) in *N,N*-dimethylformamide (320 mL). The reaction mixture was allowed to stir at ambient temperature for about 20 hours and then it was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The organics were combined, washed with brine, dried over sodium sulfate and then concentrated under reduced pressure to provide an orange oil. The oil was purified by flash chromatography (400 mL silica gel eluting initially with 10% ethyl acetate in hexane, then with 15% ethyl acetate in hexane and finally with 40% ethyl acetate in hexane) to provide 11.00 g of *N*-[2-(1-benzylpiperidin-4-yl)ethyl]-2-chloro-5,6-dimethyl-3-nitropyridin-4-amine.

10

15

Part B

Sodium hydride (1.196 g of 60%, 29.9 mmol) was added to a solution of phenol (2.81 g, 29.9 mol) in diglyme (40 mL). The mixture was stirred for 15 minutes after the cessation of gas evolution. A solution of *N*-[2-(1-benzylpiperidin-4-yl)ethyl]-2-chloro-5,6-dimethyl-3-nitropyridin-4-amine (10.9 g, 27.2 mmol) in hot diglyme was added to the phenoxide mixture. The reaction mixture was heated at reflux for 1.5 hours, cooled to ambient temperature, and then concentrated to remove the diglyme (60°C bath, 21 Pa).

20

25

The residue was purified by column chromatography eluting first with 1% methanol in dichloromethane to remove residual diglyme and then with 5% methanol in dichloromethane to elute product. The fractions were concentrated to provide 5.91 g of *N*-[2-(1-benzylpiperidin-4-yl)ethyl]-2,3-dimethyl-5-nitro-6-phenoxy-pyridin-4-amine as an orange-brown oil which solidified on standing.

Part C

Sodium borohydride (0.727 g, 19.2 mmol) was added in portions over a period of 20 minutes to a solution of nickel(II)chloride hexahydrate (1.52 g, 6.40 mmol) in methanol. A solution of the material from Part B in methanol was added dropwise over a period of 15 minutes. More sodium borohydride (50 mg) was added. The reaction mixture was filtered through a layer of filter agent and the layer of agent was washed with methanol. The filtrate was concentrated under reduced pressure. The residue was purified by chromatography (plug of silica gel eluting with 2% methanol in dichloromethane) to provide 4.6 g of *N*⁴-[2-(1-benzylpiperidin-4-yl)ethyl]-5,6-dimethyl-2-phenoxy-pyridine-3,4-diamine as an orange-brown oil which solidified on standing.

Part D

Ethoxyacetyl chloride (1.31 g, 10.7 mmol) was added dropwise to a solution of the material from Part C and triethylamine (1.64 mL, 13 mmol) in dichloromethane (60 mL). The reaction was stirred for about 20 hours and then concentrated under reduced pressure to provide crude *N*-(4-{[2-(1-benzylpiperidin-4-yl)ethyl]amino}-5,6-dimethyl-2-phenoxy-pyridin-3-yl)-2-ethoxyacetamide. The acetamide was dissolved in pyridine (60 mL), pyridine hydrochloride (1.17 g) was added and the reaction mixture was heated at reflux for 4 hours. The reaction mixture was allowed to cool to ambient temperature and then the pyridine was removed under reduced pressure. The residue was diluted with 5% sodium carbonate (100 mL) and water (50 mL) then partitioned into dichloromethane (300 mL). The organic layer was washed with water and brine, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by column chromatography eluting with 2% methanol in dichloromethane to provide 5.1 g of 1-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(ethoxymethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridine as an orange-red solid.

Part E

The material from Part D and ammonium acetate (51 g) were combined in a pressure flask (350 mL). The flask was sealed and then heated at 150°C for 24 hours followed by heating at 170°C overnight. The reaction mixture was cooled and then poured
5 into water. The resulting solution was made basic with ammonium hydroxide and then extracted with chloroform (x 2). The combined organics were washed with brine, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was dissolved in isopropanol (50 mL). Ethanesulfonic acid (21 mmol) was added dropwise and the mixture was heated at reflux for 30 minutes. The reaction was allowed to cool to
10 ambient temperature overnight and then it was concentrated under reduced pressure. The resulting oily residue was dissolved in water (200 mL), extracted with dichloromethane (x 3) and then made basic (pH 14) with 10% sodium hydroxide. The aqueous layer was extracted with chloroform (x 3). The combined organics were washed with brine, dried over magnesium sulfate and then concentrated to provide a brown oil which solidified.
15 The solid was recrystallized from acetonitrile to provide 2.54 g of a tan solid. The solid was dissolved in 2% methanol in dichloromethane and loaded onto a silica gel (130 g) column. The column was eluted with 2% methanol in dichloromethane with 1% triethylamine. The fractions were concentrated to provide 2.4 g of 1-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-
20 amine as an off-white solid.

Part F

The material from Part E was dissolved in a boiling mixture of 50/50 ethanol/methanol. The solution was allowed to cool slightly and then it was added to a Parr flask containing palladium on carbon (0.60 g) that had been wetted with ethanol.
25 The flask was placed under hydrogen pressure for about 40 hours during which time an additional 1.7 g of catalyst was added. The reaction mixture was filtered through a layer of filter agent and the filter cake was washed with methanol. The filtrate was concentrated under reduced pressure. The residue was combined with dichloromethane and then concentrated. The resulting solid was dried under high vacuum to provide 1.5 g of 2-(ethoxymethyl)-6,7-dimethyl-1-(2-piperidin-4-ylethyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine.
30

Part G

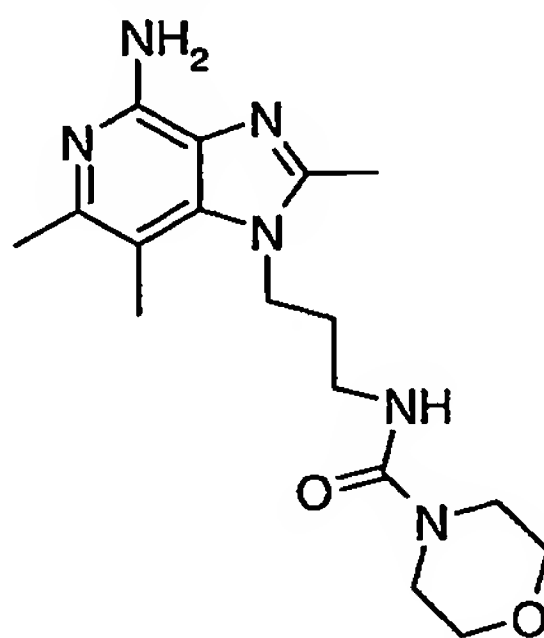
Using the general method of Example 11 Part H, 2-(ethoxymethyl)-6,7-dimethyl-1-(2-piperidin-4-ylethyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine (0.304 g, 0.917 mmol) was reacted with 4-morpholinecarbonyl chloride (0.107 mL, 0.917 mmol) to provide 0.250 g of 2-(ethoxymethyl)-6,7-dimethyl-1-{2-[1-(morpholin-4-ylcarbonyl)piperidin-4-yl]ethyl}-1*H*-imidazo[4,5-*c*]pyridin-4-amine as a yellow orange solid, m.p. 158.1-160.5°C.

Analysis: Calculated for C₂₃H₃₆N₆O₃: %C, 62.14; %H, 8.16; %N, 18.90; Found: %C, 62.02; %H, 7.94; %N, 18.99.

¹H NMR (300 MHz, DMSO-*d*₆) δ 5.82 (s, 2 H), 4.64 (s, 2 H), 4.34-4.29 (m, 2 H), 3.62-3.54 (m, 6 H), 3.50 (q, *J* = 7.0 Hz, 2 H), 3.1 (t, *J* = 4.4 Hz, 4 H), 2.74 (t, *J* = 11.8 Hz, 2 H), 2.38 (s, 3 H), 2.31 (s, 3 H), 1.67-1.55 (m, 5 H), 1.27-1.1 (m, 2 H), 1.14 (t, *J* = 7.0 Hz, 3 H); MS (CI) *m/e* 445.2935 (445.2927 calcd for C₂₃H₃₆N₆O₃, M+H).

Example 13

N-[3-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]morpholin-4-ylcarboxamide



Part A

A solution of *tert*-butyl 3-aminopropylcarbamate (121.39 g, 697 mmol) in *N,N*-dimethylformamide (200 mL) was slowly added to a solution of 2,4-dichloro-5,6-dimethyl-3-nitropyridine (110 g, 498 mmol) and triethylamine (104 mL, 746 mmol) in *N,N*-dimethylformamide (900 mL). After stirring at ambient temperature for 20 hours the reaction mixture was heated to 55°C. At 24 hours 0.1 equivalents of the carbamate was added. The reaction mixture was allowed to cool to ambient temperature overnight and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate (3

L). The solution was divided into 3 aliquots (1 L each). Each aliquot was washed with water (2 x 1 L). The pH of the aqueous washes was adjusted to 10 with potassium carbonate and then they were extracted with ethyl acetate. All of the ethyl acetate layers were combined, dried over sodium sulfate and then concentrated under reduced pressure to provide 181 g of crude product. This material was recrystallized from acetonitrile to provide 138 g of *tert*-butyl 3-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]propylcarbamate as a yellow solid.

Part B

Sodium hydride (17.23 g of 60%) was washed with hexanes to remove the mineral oil and then combined with diglyme (50 mL). Under a nitrogen atmosphere the mixture was cooled. A solution of phenol (35.82 g, 408 mmol) in diglyme (150 mL) was added dropwise. The reaction mixture was stirred for 15 minutes after the cessation of gas evolution. The material from Part A was added. The reaction mixture was heated at 62°C for several days, then the temperature was increased to 120°C and the reaction was stirred overnight. The reaction mixture was allowed to cool to ambient temperature, then it was combined with water (4 L), stirred for about 4.5 hours and then allowed to stand overnight. The solids were dissolved in ethyl acetate and then filtered to remove particulates. The filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (~2 L), washed with saturated potassium carbonate (3 x 2 L), dried over magnesium sulfate and then concentrated under reduced pressure to provide 152.3 g of *tert*-butyl 3-[(2,3-dimethyl-5-nitro-6-phenoxy-pyridin-4-yl)amino]propylcarbamate.

Part C

A mixture of 5% Pt/C (85 g) and toluene (50 mL) was added to a solution of the material from Part B in a mixture of toluene (1850 mL) and isopropanol (125 mL) in a hydrogenation flask. The flask was placed under a hydrogen atmosphere overnight. Another 22.5 g of catalyst was added and the flask was placed back on the hydrogenator. After 6 hours catalyst (40 g) and isopropanol (50 mL) were added. The flask was placed back on the hydrogenator overnight. The reaction mixture was filtered to remove the catalyst. The filtrate was concentrated under reduced pressure to provide *tert*-butyl 3-[(3-amino-5,6-dimethyl-2-phenoxy-pyridin-4-yl)amino]propylcarbamate as an oil. The oil was dissolved in pyridine (1300 mL).

Part D

A portion (650 mL) of the pyridine solution from Part C was cooled in an ice bath for 10 minutes. Acetyl chloride (12.65 mmol, 0.1779 mmol) was slowly added over a period of 5 minutes. The reaction mixture was removed from the ice bath and heated to reflux. The temperature was reduced to 110°C and the reaction mixture was stirred overnight. The pyridine was removed under reduced pressure. The residue was slurried with heptane and then concentrated under reduced pressure. The residue was combined with ethyl acetate (1 L) and water (1 L). The pH was adjusted to 12 with 50% sodium hydroxide and the layers were separated. The organic layer was filtered to remove particulates and then concentrated under reduced pressure. The residue was purified by ethyl acetate slurry to provide 39.8 g of *tert*-butyl 3-(2,6,7-trimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propylcarbamate as a light brown fluffy solid.

Part E

The material from Part D was combined with ammonium acetate (410 g) in a 2 L flask. A wad of paper towels was stuffed into the neck of the flask. The reaction mixture was heated with stirring at 145°C for 20.5 hours. The reaction mixture was allowed to cool to ambient temperature, the pH was adjusted to 11 with ammonium hydroxide and the mixture was extracted with chloroform. The extract was washed with 1% sodium carbonate (7 x 1 L). The original aqueous phase and the first three washes were combined, filtered to remove particulates and then concentrated to a volume of about 1 L. This solution was run overnight on a continuous extraction apparatus with chloroform. The chloroform extract was concentrated under reduced pressure to provide 27.1 g of an off-white solid. This material was slurried with methyl acetate to provide about 16.5 g of *N*-[3-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]acetamide. A portion (0.5 g) was recrystallized from acetonitrile to provide about 0.3 g of the pure acetamide as a white solid, m.p. 181.4–182.1°C. Analysis: Calculated for C₁₄H₂₁N₅O • 0.50 H₂O: %C, 59.13; %H, 7.80; %N, 24.63; Found: %C, 59.08; %H, 8.00; %N, 24.73.

Part F

Concentrated hydrochloric acid (5 mL) was slowly added to a solution of *N*-[3-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]acetamide (15.94 g, 57.9 mmol) in absolute ethanol (100 mL). A precipitate formed immediately and the mixture thickened. Ethanol (50 mL) was added followed by the addition of concentrated

hydrochloric acid (119.5 mL). The reaction mixture was heated at reflux for 2 days. The solvents were removed under reduced pressure. Water (250 mL) was added to the residue, solid potassium carbonate was added until the pH reached 7 at which time chloroform (250 mL) was added. Sodium carbonate addition was resumed until the pH reached 10, then 50% sodium hydroxide was added until the pH reached 14. The mixture was diluted with additional chloroform (500 mL) and then stirred at ambient temperature for 2 days. The organic layer was separated, dried with magnesium sulfate and then concentrated under reduced pressure. The residue was recrystallized from acetonitrile to provide 8.42 g of 1-(3-aminopropyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine as an off-white crystalline solid, m.p. 191.5-191.9°C. Analysis: Calculated for C₁₂H₁₉N₅ • 0.25 H₂O: %C, 60.61; %H, 8.26; %N, 29.45; Found: %C, 60.50; %H, 8.28; %N, 29.57.

Part G

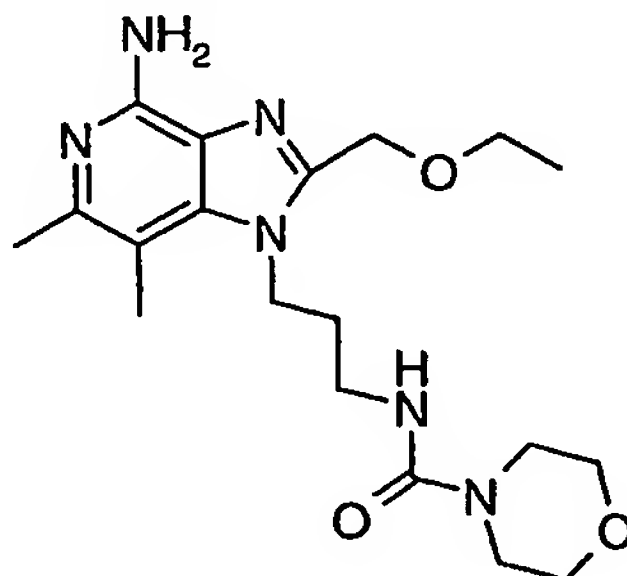
Triethylamine (0.78 mL, 5.6 mmol) was added to a solution of 1-(3-aminopropyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (1.00 g, 4.3 mmol) in chloroform (50 mL). The solution was cooled in an ice bath and then 4-morpholinecarbonyl chloride (0.55 mL, 4.7 mmol) was added. After 15 minutes the reaction mixture was removed from the ice bath and allowed to stir at ambient temperature for 2 days. The reaction mixture was diluted with water (30 mL) and the pH was adjusted to 11 with potassium carbonate. The resulting precipitate was isolated by filtration and then recrystallized from isopropanol/water to provide 0.61 g of N-[3-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]morpholine-4-carboxamide as a white solid, m.p. 128.9-129.7°C. Analysis: Calculated for C₁₇H₂₆N₆O₂ • 1.00 H₂O: %C, 56.03; %H, 7.74; %N, 23.06; Found: %C, 56.10; %H, 7.92; %N, 23.31.

¹H NMR (Bruker 300 MHz, DMSO-*d*₆) δ 6.63 (t, *J*=4.9 Hz, 1 H), 5.56 (s, 2 H), 4.19 (t, *J*=8.1 Hz, 2 H), 3.53 (t, *J*=4.4 Hz, 4 H), 3.25 (t, *J*=4.9 Hz, 4 H), 3.14 (q, *J*=6.2 Hz, 2 H), 2.45 (s, 3 H), 2.35 (s, 3 H), 2.29 (s, 3 H), 1.81 (p, *J*=7.4 Hz, 2 H).

MS(CI) *m/e* 347 (M+H).

Example 14

N-{3-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propyl}morpholin-4-ylcarboxamide



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Part A

Using the general method of Example 13 Part D, a pyridine solution of *tert*-butyl 3-[(3-amino-5,6-dimethyl-2-phenoxy-4-yl)amino]propylcarbamate (see Example 13 Part C) was treated with ethoxyacetyl chloride (21.81 g, 178 mmol). The crude product was combined with dichloromethane (2 L) and water (2 L). The pH was adjusted to 12 with 50% sodium hydroxide and the mixture was stirred for 30 minutes. The organic phase was separated, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was diluted with heptane and then concentrated to remove residual pyridine. This procedure was repeated several times to provide 64.8 g of *tert*-butyl 3-[2-(ethoxymethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propylcarbamate as a brown tar.

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Part B

Ammonium acetate (500 g) and *tert*-butyl 3-[2-(ethoxymethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propylcarbamate (35.09 g, 77 mmol) were combined in a 2 L flask. The neck of the flask was stuffed with a wad of paper towels. The reaction mixture was heated with stirring at 150°C for 27 hours. The reaction mixture was allowed to cool to ambient temperature and then it was placed in an ice bath. Ammonium hydroxide was added until the pH reached 11. Sodium hydroxide (50%) was added until the pH reached 14. The resulting precipitate was isolated by filtration and then dissolved in chloroform (4 L). The chloroform solution was divided into two portions and each was washed with saturated potassium carbonate (2 x 2 L). The organics were combined, dried over magnesium sulfate and then concentrated under reduced pressure to

25

provide 30.3 g of crude product. This material was slurried with methyl acetate to provide 13.7 g of *N*-{3-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propyl}acetamide as a gray solid, m.p. 161.8-162.3°C

Analysis: Calculated for C₁₆H₂₅N₅O₂: %C, 60.17; %H, 7.89; %N, 21.93; Found: %C, 59.97; %H, 7.70; %N, 22.19.

Part C

Using the general method of Example 13 Part F, *N*-{3-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propyl}acetamide (13.14 g, 4.1 mmol) was hydrolyzed and purified to provide 10.81 g of 1-(3-aminopropyl)-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine as a brown solid, m.p. 126.8-127.2°C.

Analysis: Calculated for C₁₄H₂₃N₅O: %C, 60.62; %H, 8.36; %N, 25.25; Found: %C, 60.49; %H, 8.38; %N, 25.33.

Part D

Using the general method of Example 13 Part G, 1-(3-aminopropyl)-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (1.00 g, 3.6 mmol) was reacted with 4-morpholinylcarbonyl chloride (0.46 mL, 40 mmol) to provide 1.05 g of *N*-{3-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propyl}morpholine-4-carboxamide as an off white solid, m.p. 140.5-142.2°C.

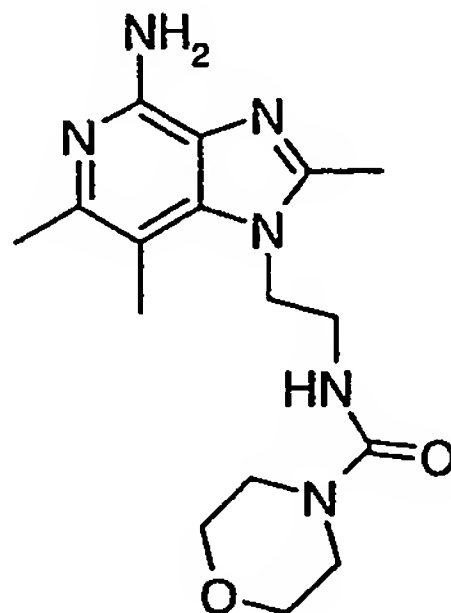
Analysis: Calculated for C₁₉H₃₀N₆O₃ • 1.00 H₂O: %C, 55.86; %H, 7.90; %N, 20.57; Found: %C, 55.60; %H, 7.87; %N, 20.59.

¹H NMR (Bruker 300 MHz, DMSO-*d*₆) δ 6.64 (t, *J*=5.6 Hz, 1 H), 5.75 (s, 2 H), 4.62 (s, 2 H), 4.28 (t, *J*=8.1 Hz, 2 H), 3.54 (t, *J*=4.9 Hz, 4 H), 3.51 (q, *J*=6.9 Hz, 2 H), 3.25 (t, *J*=4.9 Hz, 4 H), 3.15 (q, *J*=5.6 Hz, 2 H), 2.36 (s, 3 H), 2.30 (s, 3 H), 1.87 (p, *J*=8.1 Hz, 2 H), 1.13 (t, *J*=7.5 Hz, 3 H).

MS(CI) *m/e* 276 (M+H).

Example 15

N-[2-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)ethyl]morpholin-4-ylcarboxamide



5

Part A

A solution of 2,4-dichloro-5,6-dimethyl-3-nitropyridine (60 g, 271 mmol) in anhydrous N,N-dimethylformamide (600 mL) was cooled to 0°C. Triethylamine (44.8 mL, 326 mmol) was added drop wise followed by *tert*-butyl 2-aminoethylcarbamate (52.2 g, 326 mmol). After 30 minutes the ice bath was removed and the reaction mixture was heated to 60°C. The reaction was heated at 60°C overnight and then it was concentrated under reduced pressure to provide an orange oil. The oil was dissolved in ethyl acetate (1 L), washed with water (3 x 500 mL), dried over magnesium sulfate and then concentrated under reduced pressure to provide a yellow oil. The oil was triturated with methanol (~100 mL). The resulting solid was isolated by filtration and washed with cold methanol to provide 72.3 g of *tert*-butyl 2-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]ethylcarbamate as a solid.

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Part B

Phenol (1.19 g, 12.6 mmol) was added in portions to a chilled (0°C) suspension of sodium hydride (0.52 g of 60%, 13.1 mmol) in diglyme (4 mL). The reaction mixture was then stirred for 30 minutes. A warm solution of *tert*-butyl 2-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]ethylcarbamate (3.0 g, 8.70 mmol) in diglyme (6 mL) was added and the reaction mixture was heated at 90°C overnight. The reaction mixture was cooled and poured slowly into water (100 mL). The resulting tan solid was isolated by filtration, washed with water, dried and then recrystallized from isopropanol (25 mL) to provide 2.07 g of *tert*-butyl 2-[(2,3-dimethyl-5-nitro-6-phenoxy-pyridin-4-yl)amino]ethylcarbamate as

20

25

white needles. The reaction was repeated using 66.5 g of starting material to provide 50.4 g of product as white needles, m.p. 158-160°C..

Part C

Catalyst (5 g of 5% platinum on carbon) was added to a warm solution of *tert*-butyl 2-[(2,3-dimethyl-5-nitro-6-phenoxy-pyridin-4-yl)amino]ethylcarbamate (50.4 g) in a mixture of toluene (500 mL) and methanol (40 mL). The mixture was placed under hydrogen pressure (50 psi, 3.4×10^5 Pa). After 2 hours more catalyst (4 g) was added and the hydrogenation continued overnight. The reaction mixture was filtered through a layer of Celite® filter aid and the filter cake was washed with hot toluene (1 L). The filtrate was concentrated under reduced pressure to provide 45.1 g of *tert*-butyl 2-[(3-amino-5,6-dimethyl-2-phenoxy-pyridin-4-yl)amino]ethylcarbamate as a white solid.

Part D

A mixture of *tert*-butyl 2-[(3-amino-5,6-dimethyl-2-phenoxy-pyridin-4-yl)amino]ethylcarbamate (43.7 g, 117 mmol), triethyl orthoacetate (22.6 mL, 123 mmol), pyridine hydrochloride (4.4 g) and toluene (440 mL) was heated at reflux for 30 minutes. The reaction mixture was concentrated under reduced pressure to provide a brown oil. The oil was dissolved in ethyl acetate (1 L) and washed with water (2 x 500 mL). The aqueous washes were combined and extracted with ethyl acetate (2 x 500 mL). The combined organics were washed with brine, dried over magnesium sulfate and then concentrated under reduced pressure to provide 46.4 g of *tert*-butyl 2-(2,6,7-trimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)ethylcarbamate as a white solid, m.p. 180-182°C.

Part E

A mixture of ammonium acetate (95 g) and *tert*-butyl 2-(2,6,7-trimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)ethylcarbamate (9.5 g) was heated at 160°C in a sealed tube for 24 hours. The reaction mixture was allowed to cool to ambient temperature and then it was partitioned between water and chloroform. The aqueous layer was made basic (pH 13) with 50% sodium hydroxide and then extracted with chloroform (10 x 400 mL). The combined organics were dried over magnesium sulfate and then concentrated under reduced pressure to provide a brown solid. The solid was dissolved in warm isopropanol (80 mL) and then combined with 1M hydrochloric acid in diethyl ether (23.7 mL). The resulting precipitate was isolated by filtration, washed with cold isopropanol and diethyl ether, and then dried in a vacuum oven at 80°C overnight to

provide 5.0 g of N-[2-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)ethyl]acetamide hydrochloride as a white solid, m.p.>250°C. Analysis: Calculated for: C₁₃H₁₉N₅O • 1.00 HCl: %C, 52.43; %H, 6.77; %N, 23.52; Found: %C, 52.25; %H, 6.81; %N, 23.41.

- 5 The reaction was repeated using 34 g of starting material to provide 18 g of the acetamide hydrochloride as a light tan solid.

Part F

- N-[2-(4-Amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)ethyl]acetamide hydrochloride (18 g), concentrated hydrochloric acid (231 mL) and ethanol (350 mL) were
10 combined and heated at 90°C overnight. The reaction mixture was allowed to cool to ambient temperature and then it was diluted with diethyl ether (200 mL). The resulting precipitate was isolated by filtration, washed with cold ethanol and with diethyl ether, and then dried under vacuum at 80°C overnight to provide 17.3 g of 1-(2-aminoethyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine hydrochloride as white needles. Analysis:
15 Calculated for C₁₁H₁₇N₅ • 2.8 HCl • 0.25 H₂O: %C, 40.32; %H, 6.26; %N, 30.83; Found: %C, 40.54; %H, 6.15; %N, 30.87.

Part G

- 4-Morpholinecarbonyl chloride (1.42 mL, 12.2 mmol) was added to a mixture of 1-(2-aminoethyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine hydrochloride (4.0 g
20 of Part F, 12.2 mmol), triethylamine (85 mL, 610 mmol) and dichloromethane (400 mL) and the reaction mixture was allowed to stir overnight. The next day more 4-morpholinecarbonyl chloride (0.25 eq) was added and the reaction mixture was allowed to stir overnight. The solvents were removed under reduced pressure to provide a white solid. This material was dissolved in water (200 mL), treated with sodium carbonate (5 g),
25 and then extracted with chloroform (5 x 500 mL). The combined extracts were dried over magnesium sulfate and then concentrated under reduced pressure to provide a white solid. The solid was dissolved in warm isopropanol, cooled and then combined with 12.2 mL of 1 M hydrochloric acid in diethyl ether. The resulting precipitate was isolated by filtration, washed with isopropanol and diethyl ether, and dried to provide the hydrochloride salt of
30 the desired product. The salt was dissolved in water (50 mL) and then combined with excess sodium carbonate (4 g). The resulting precipitate was isolated by filtration, washed with water, and then dried in a vacuum oven at 90°C overnight to provide 2.3 g of N-[2-

(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)ethyl]morpholine-4-carboxamide as a white solid, m.p. 219-221°C.

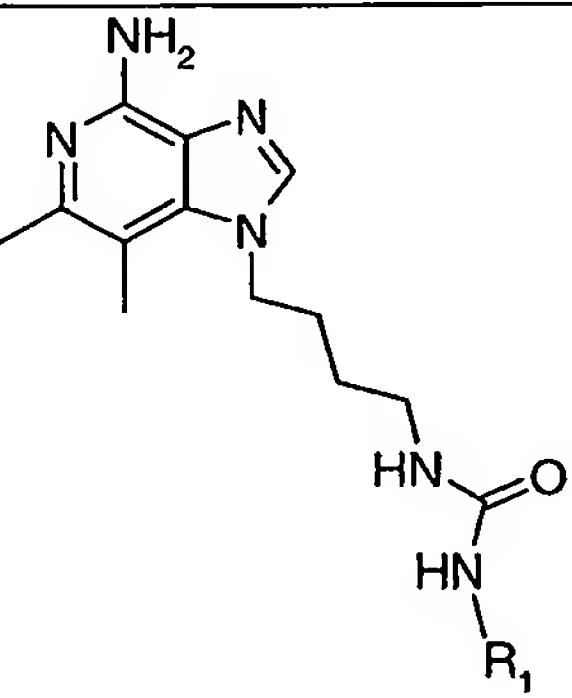
Analysis: Calculated for C₁₆H₂₄N₆O₂: %C, 57.81; %H, 7.28; %N, 25.28; Found: %C, 58.13; %H, 7.14; %N, 25.56.

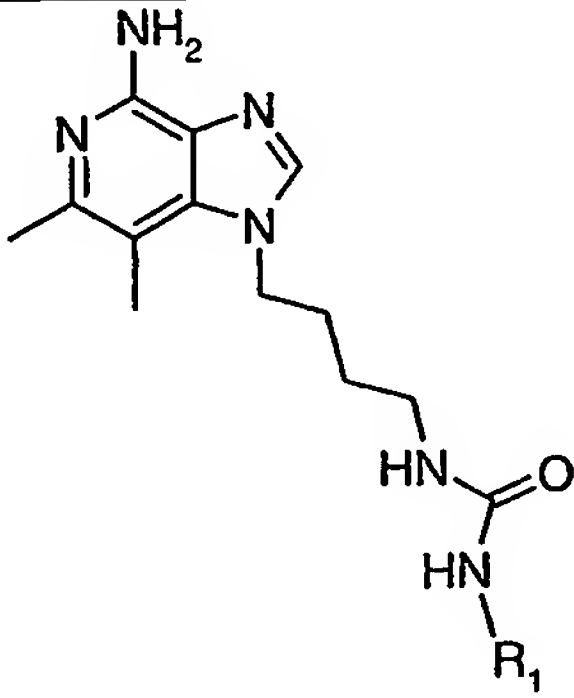
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Examples 16 – 26

The compounds in the table below were prepared using the following method. The appropriate isocyanate (1.1 eq.) was added to a test tube containing a solution of 1-(4-aminobutyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (25 mg, see Example 11, Part G) in chloroform (5 mL). The test tube was capped and then placed on a shaker at ambient temperature overnight. The solvent was removed by vacuum centrifugation. The residue was purified by prep HPLC using the method described above to provide the trifluoroacetate salt of the desired compound. The table below shows the structure of the free base and the observed accurate mass (m + H). The structures were confirmed by ¹H NMR spectroscopy.

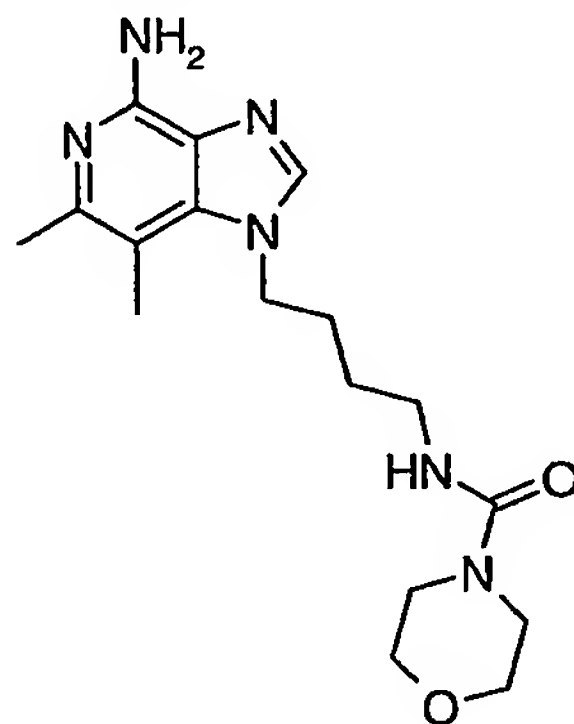
15

		
Example Number	R ₁	Accurate Mass (obs.)
16	1-methylethyl	319.2256
17	1,1-dimethylethyl	333.2404
18	butyl	333.2414
19	phenyl	353.2086
20	cyclohexyl	359.2569
21	3-cyanophenyl	378.2058

		
Example Number	R ₁	Accurate Mass (obs.)
22	3-methoxyphenyl	383.2204
23	3-acetylphenyl	395.2217
24	4-(dimethylamino)phenyl	396.2537
25	3-(methylthio)phenyl	399.1985
26	2,4-dimethoxyphenyl	413.2327

Example 27

N-[4-(4-amino-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]morpholin-4-ylcarboxamide



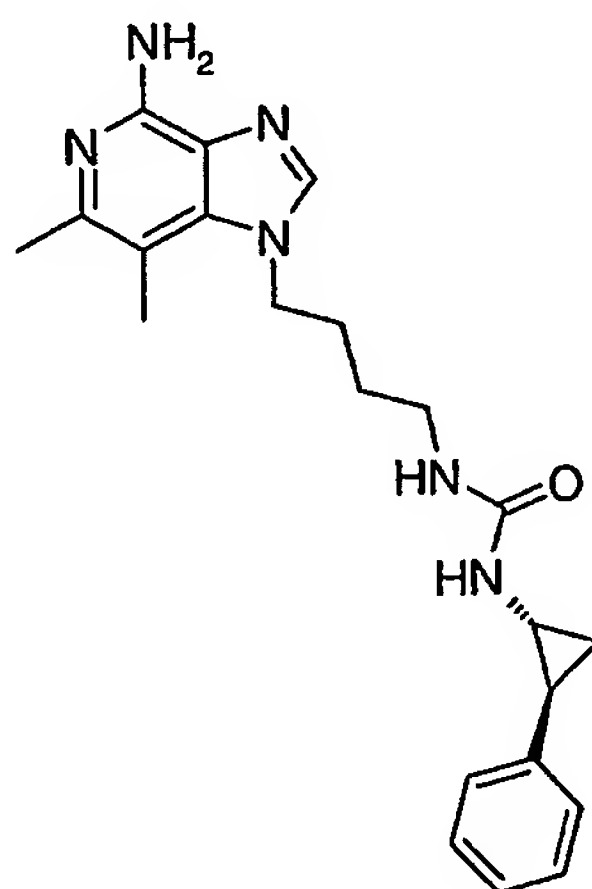
5

Using the method of Examples 16 – 26, 4-morpholinecarbonyl chloride was reacted with 1-(4-aminobutyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 347.2214.

10

Example 28

N-[4-(4-amino-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-*N'*-[(1*R*^{*},2*S*^{*})-2-phenylcyclopropyl]urea



5

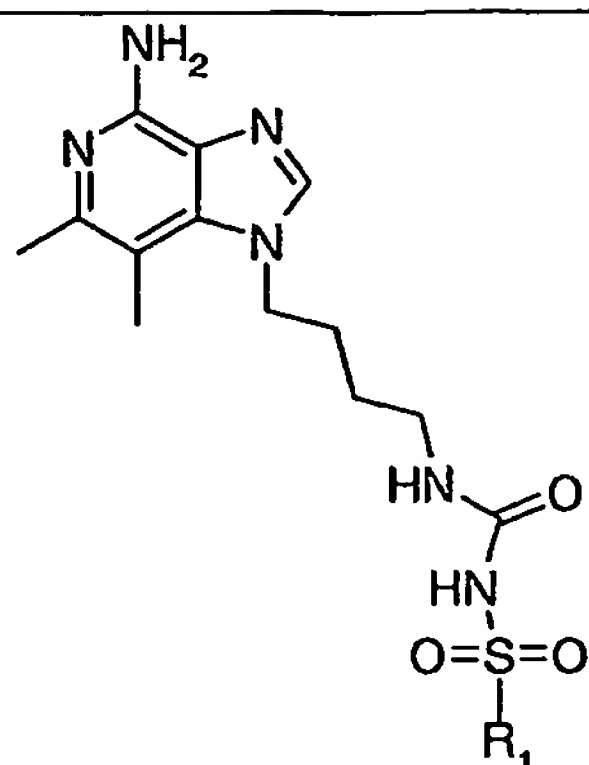
Using the method of Examples 16 – 26, trans-2-phenylcyclopropyl isocyanate was reacted with 1-(4-aminobutyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 393.2425.

10

Examples 29-31

The compounds in the table below were prepared using the method of Examples 16 – 26. The appropriate sulfonyl isocyanate was reacted with 1-(4-aminobutyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound.

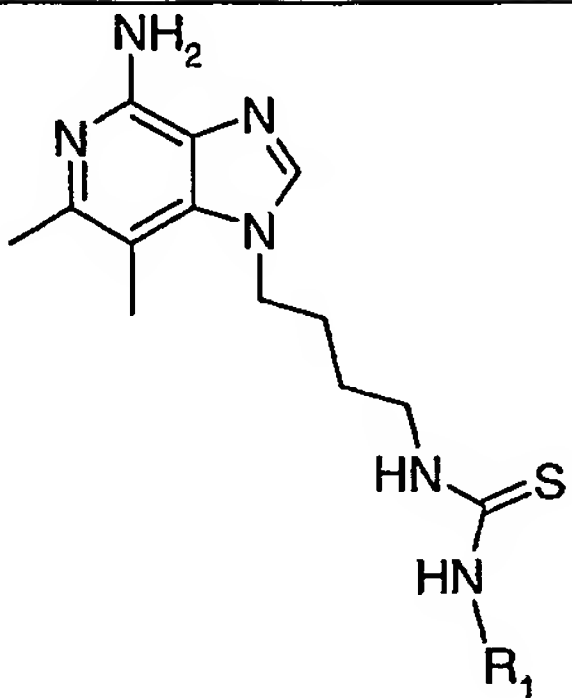
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Example Number	R ₁	Accurate Mass (obs.)
29	phenyl	417.1702
30	4-methylphenyl	431.1868
31	4-chlorophenyl	451.1338

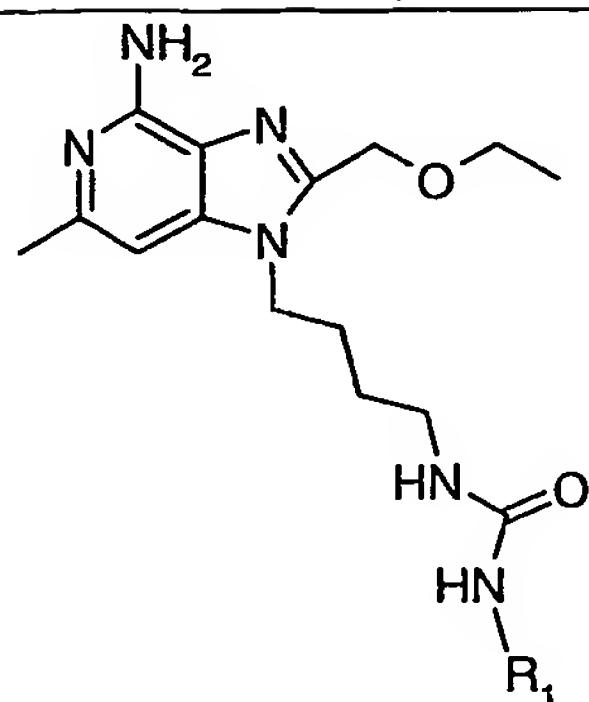
Examples 32 – 35

The compounds in the table below were prepared using the method of Examples 16–26. The appropriate thioisocyanate was reacted with 1-(4-aminobutyl)-6,7-dimethyl-1H-imidazo[4,5-c]pyridin-4-amine to provide the desired compound.

		
Example Number	R ₁	Accurate Mass (obs.)
32	methyl	307.1699
33	phenyl	369.1868
34	2-phenylethyl	397.2194
35	4-methoxyphenyl	399.1994

Examples 36 – 45

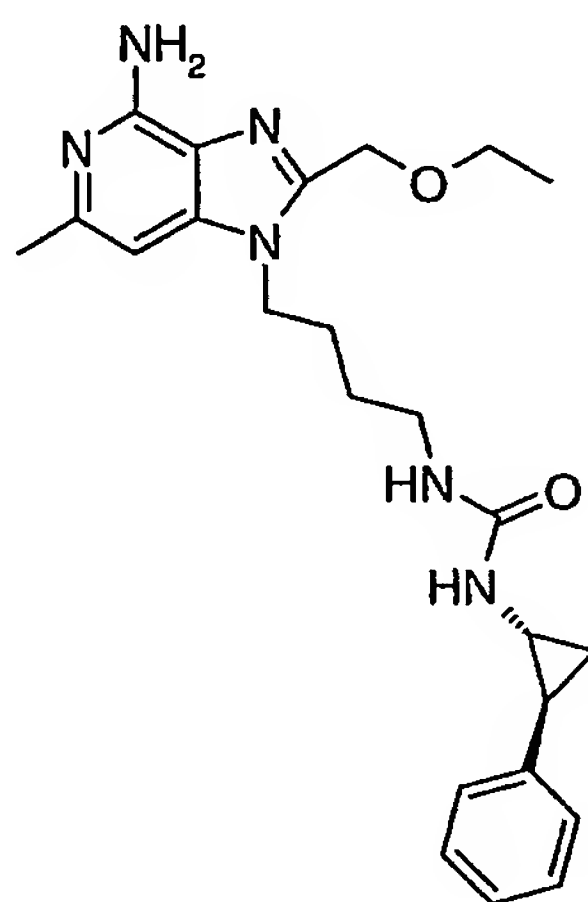
The compounds in the table below were prepared using the following method. The appropriate isocyanate (1.1 eq.) was added to a test tube containing a solution of 1-(4-aminobutyl)-2-ethoxymethyl-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (25 mg; see Example 10, Part I) in chloroform (5 mL). The test tube was capped and then placed on a shaker at ambient temperature for 16 hours. The solvent was removed by vacuum centrifugation. The residue was purified by prep HPLC using the method described above to provide the trifluoroacetate salt of the desired compound. The structures were confirmed by ¹H NMR spectroscopy. The table below shows the structure of the free base and the observed accurate mass (m + H).



Example Number	R ₁	Accurate Mass (obs.)
36	1-methylethyl	363.2521
37	1,1-dimethylethyl	377.2675
38	butyl	377.2671
39	phenyl	397.2360
40	ethoxycarbonylmethyl	407.2418
41	3-cyanophenyl	422.2313
42	3-acetylphenyl	439.2477
43	4-(dimethylamino)phenyl	440.2787
44	3-(methylthio)phenyl	443.2253
45	2,4-dimethoxyphenyl	457.2559

Example 46

N-{4-[4-amino-2-(ethoxymethyl)-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}-*N'*-[(1*R*^{*},2*S*^{*})-2-phenylcyclopropyl]urea



5

Using the method of Examples 36 – 45, trans-2-phenylcyclopropyl isocyanate was reacted with 1-(4-aminobutyl)-2-ethoxymethyl-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 437.2666.

10

Examples 47 – 48

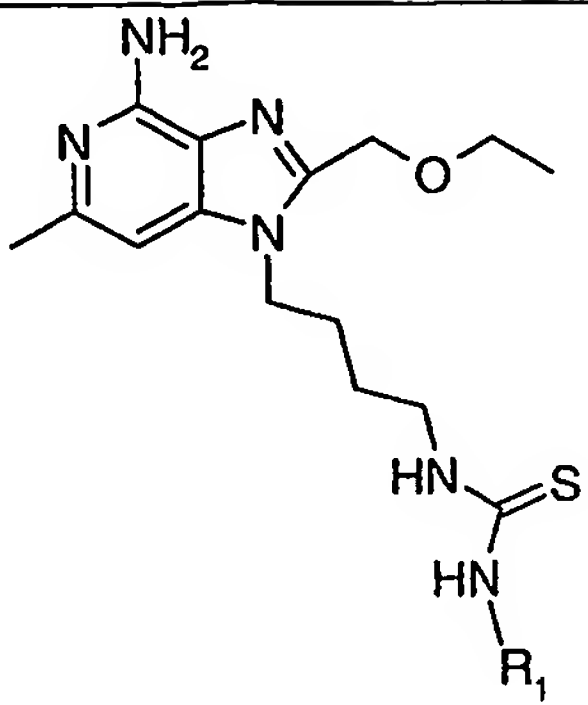
The compounds in the table below were prepared using the method of Examples 36 – 45. The appropriate sulfonyl isocyanate was reacted with 1-(4-aminobutyl)-2-ethoxymethyl-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound.

15

Example Number	R ₁	Accurate Mass (obs.)
47	phenyl	461.1974
48	4-methylphenyl	475.2144

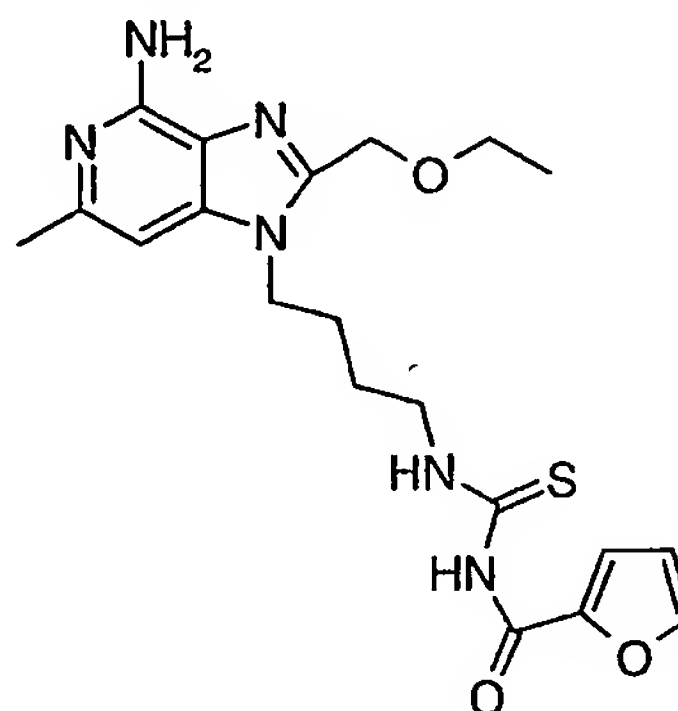
Examples 49 – 52

The compounds in the table below were prepared using the method of Examples 36–45. The appropriate isothiocyanate was reacted with 1-(4-aminobutyl)-2-ethoxymethyl-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound.

		
Example Number	R ₁	Accurate Mass (obs.)
49	methyl	351.1976
50	phenyl	413.2144
51	2-phenylethyl	441.2240
52	4-methoxyphenyl	443.2248

Example 53

N-(4-[4-amino-2-(ethoxymethyl)-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl)-*N'*-(2-furoyl)thiourea



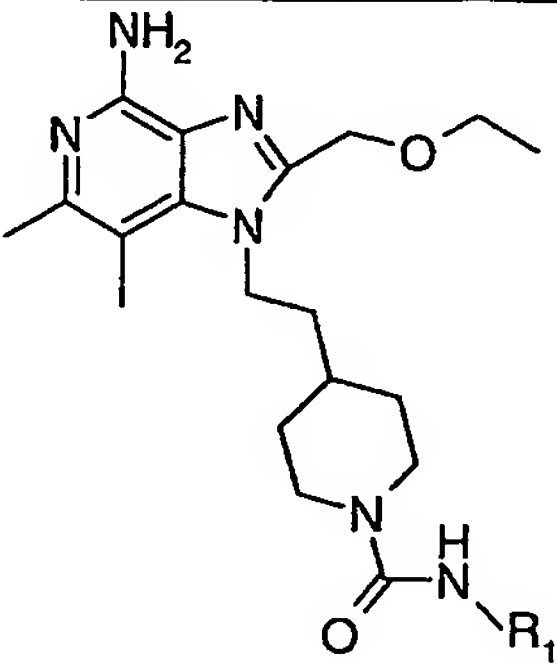
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Using the method of Examples 36 – 45, 2-furoylisothiocyanate was reacted with 1-(4-aminobutyl)-2-ethoxymethyl-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 431.887.

10

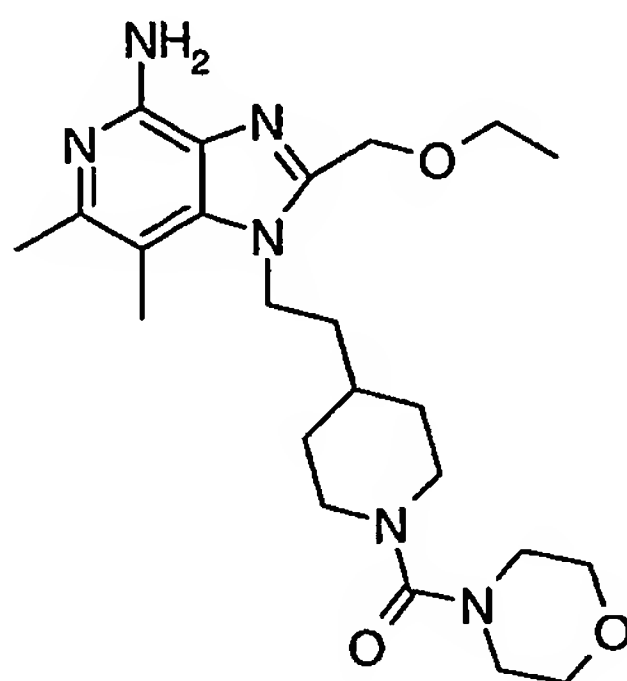
Examples 54 – 65

The compounds in the table below were prepared using the following method. The appropriate isocyanate (1.1 eq.) was added to a test tube containing a solution of 2-(ethoxymethyl)-6,7-dimethyl-1-(2-piperidin-4-ylethyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine (25 mg; see Example 12 Part F) in chloroform (5 mL). The test tube was capped and then placed on a shaker at ambient temperature for 16 hours. The solvent was removed by vacuum centrifugation. The residue was purified by prep HPLC using the method described above to provide the trifluoroacetate salt of the desired compound. The structures were confirmed by ¹H NMR spectroscopy. The table below shows the structure of the free base and the observed accurate mass (m + H).

		
Example Number	R ₁	Accurate Mass (obs.)
54	1-methylethyl	417.3003
55	1,1-dimethylethyl	431.3138
56	butyl	431.3129
57	phenyl	451.2849
58	cyclohexyl	457.3306
59	ethoxycarbonylmethyl	461.2898
60	3-cyanophenyl	476.2797
61	3-methoxyphenyl	481.2950
62	3-acetylphenyl	493.2955
63	4-(dimethylamino)phenyl	494.3234
64	3-(methylthio)phenyl	497.2724
65	2,4-dimethoxyphenyl	511.3029

Example 66

2-(ethoxymethyl)-6,7-dimethyl-1-{2-[1-(morpholin-4-ylcarbonyl)piperidin-4-yl]ethyl}-
1*H*-imidazo[4,5-*c*]pyridin-4-amine



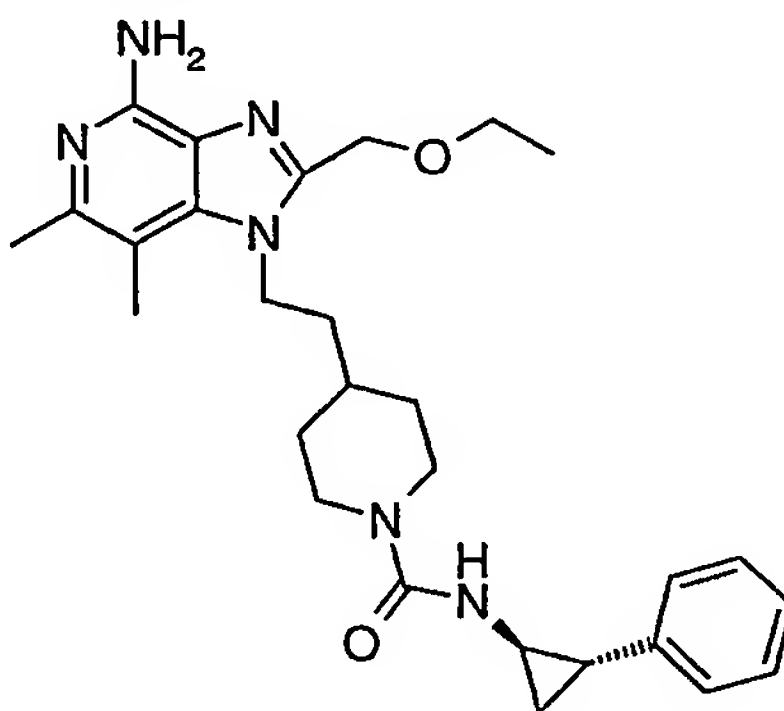
5

Using the method of Examples 54 – 65, 4-morpholinecarbonyl chloride was reacted with 2-(ethoxymethyl)-6,7-dimethyl-1-(2-piperidin-4-ylethyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 445.2929.

10

Example 67

4-{2-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]ethyl}-*N*-[(1*R*^{*},2*S*^{*})-2-phenylcyclopropyl]piperidine-1-carboxamide

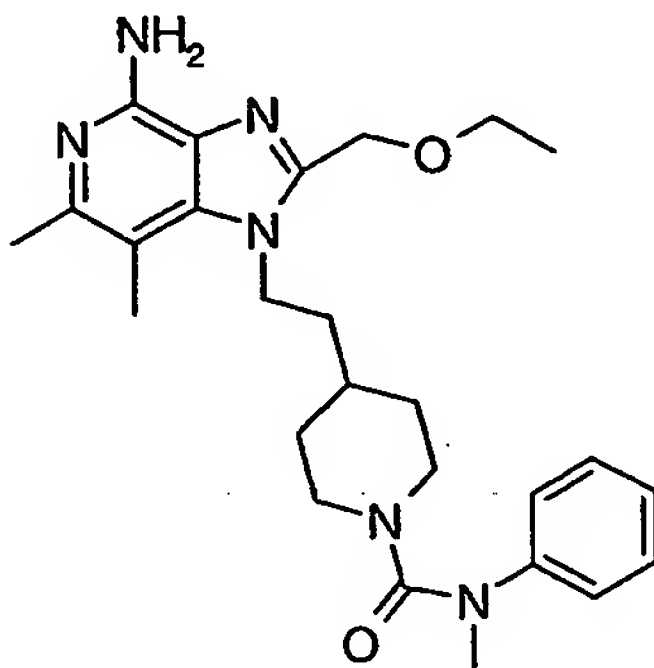


15

Using the method of Examples 54 – 65, trans-2-phenylcyclopropyl isocyanate was reacted with 2-(ethoxymethyl)-6,7-dimethyl-1-(2-piperidin-4-ylethyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 491.3139.

Example 68

4-{2-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]ethyl}-*N*-methyl-*N*-phenylpiperidine-1-carboxamide



5

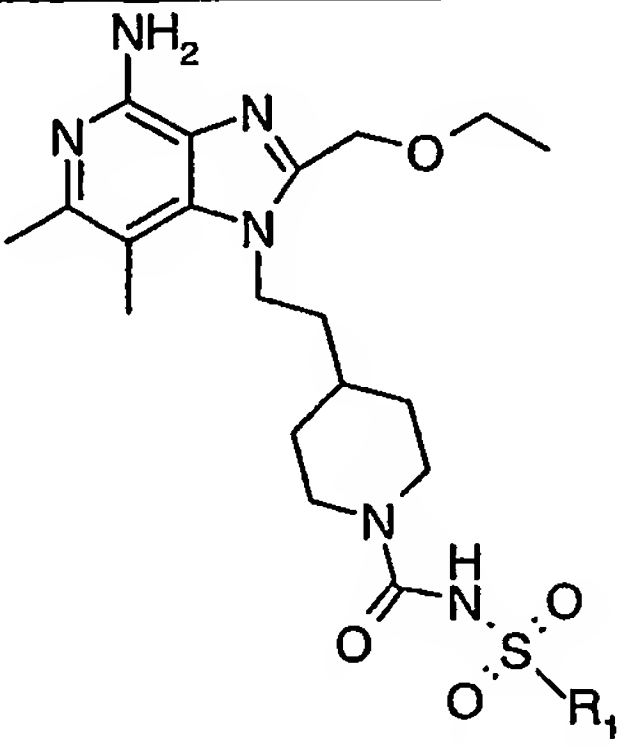
Using the method of Examples 54 – 65, *N*-methyl-*N*-phenylcarbamoyl chloride was reacted with 2-(ethoxymethyl)-6,7-dimethyl-1-(2-piperidin-4-ylethyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 465.3006.

10

Examples 69 – 70

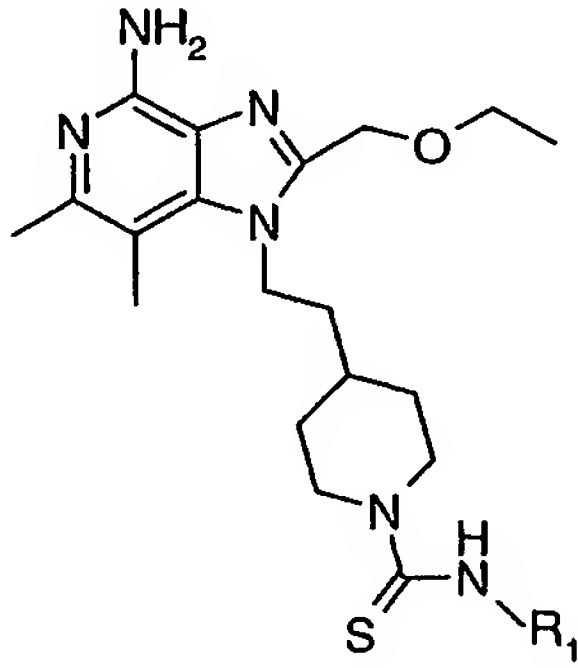
The compounds in the table below were prepared using the method of Examples 54 – 65. The appropriate sulfonyl isocyanate was reacted with 2-(ethoxymethyl)-6,7-dimethyl-1-(2-piperidin-4-ylethyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound.

15

		
Example Number	R ₁	Accurate Mass (obs.)
69	phenyl	515.2443
70	4-chlorophenyl	549.2064

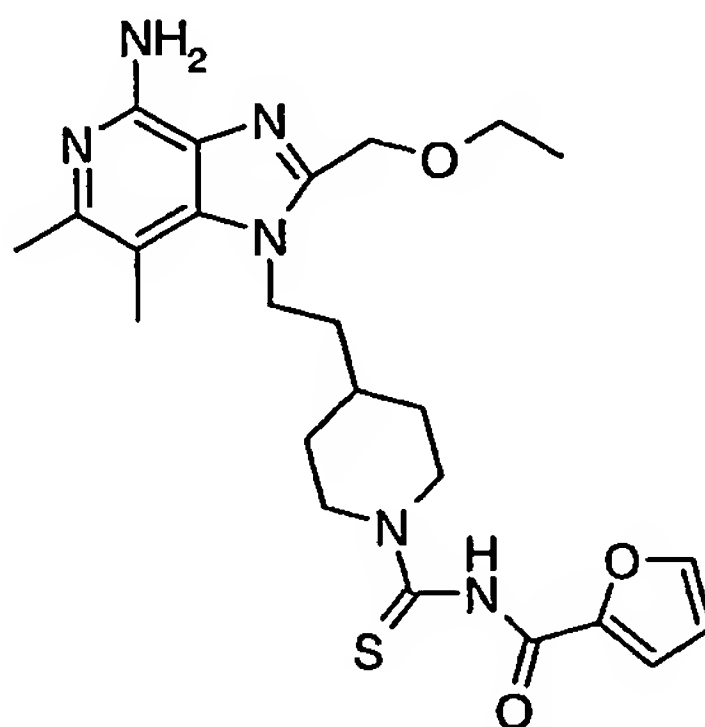
Examples 71 – 73

The compounds in the table below were prepared using the method of Examples 54 – 65. The appropriate isothiocyanate was reacted with 2-(ethoxymethyl)-6,7-dimethyl-1-(2-piperidin-4-ylethyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound.

		
Example Number	R ₁	Accurate Mass (obs.)
71	phenyl	467.2610
72	2-phenylethyl	495.2918
73	4-methoxyphenyl	497.2700

Example 74

N-[(4-{2-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]ethyl}piperidin-1-yl)carbonothioyl]-2-furamide



5

Using the method of Examples 54 – 65, 2-furoylisothiocyanate was reacted with 2-(ethoxymethyl)-6,7-dimethyl-1-(2-piperidin-4-ylethyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 485.2357.

10

Examples 75- 85

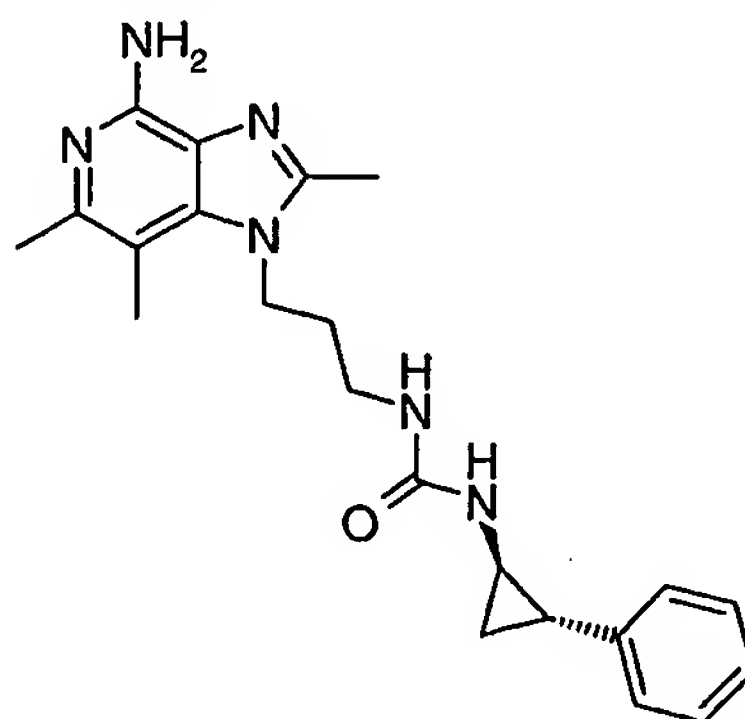
15

The compounds in the table below were prepared using the following method. The appropriate isocyanate (1.1 eq.) was added to a test tube containing a solution of 1-(3-aminopropyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (25 mg; see Example 13 Part F) in chloroform (5 mL). The test tube was capped, vortexed and then placed on a shaker at ambient temperature for 16 hours. The solvent was removed by vacuum centrifugation. The residue was purified by prep HPLC using the method described above to provide the trifluoroacetate salt of the desired compound. The table below shows the structure of the free base and the observed accurate mass (*m* + *H*).

Example Number	R ₁	Accurate Mass (obs.)
75	1-methylethyl	319.2243
76	butyl	333.2394
77	phenyl	353.2086
78	cyclohexyl	359.2569
79	ethoxycarbonylmethyl	363.2152
80	3-cyanophenyl	378.2023
81	3-methoxyphenyl	383.2190
82	3-acetylphenyl	395.2192
83	4-(dimethylamino)phenyl	396.2512
84	3-(methylthio)phenyl	399.1985
85	2,4-dimethoxyphenyl	413.2290

Example 86

N-[3-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]-*N'*-[(1*R*^{*},2*S*^{*})-2-phenylcyclopropyl]urea

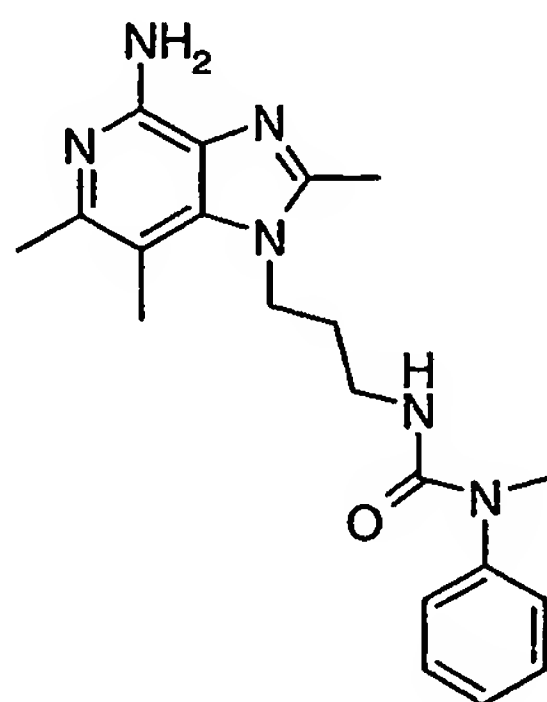


Using the methods of Examples 75 –85, trans-2-phenylcyclopropyl isocyanate was reacted with 1-(3-aminopropyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 393.2393.

5

Example 87

N'-[3-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]-*N*-methyl-*N*-phenylurea



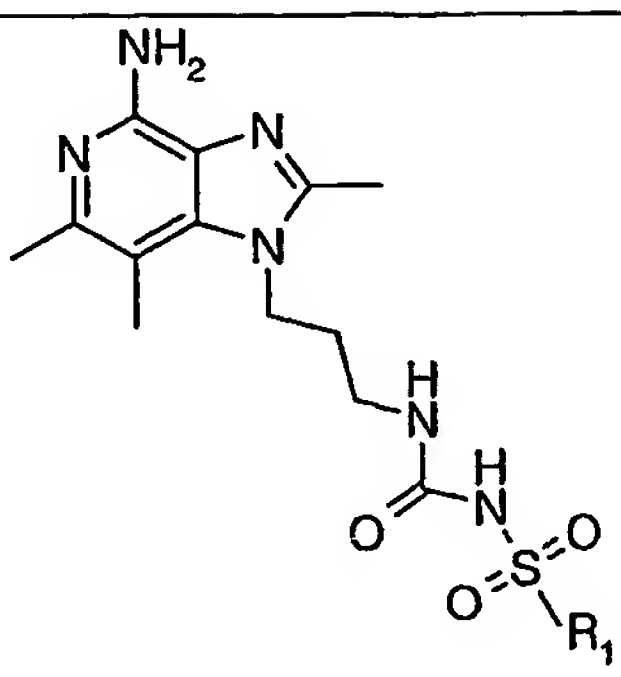
10

Using the methods of Examples 75 –85, *N*-methyl-*N*-phenylcarbamoyl chloride was reacted with 1-(3-aminopropyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 367.2263.

Examples 88 – 89

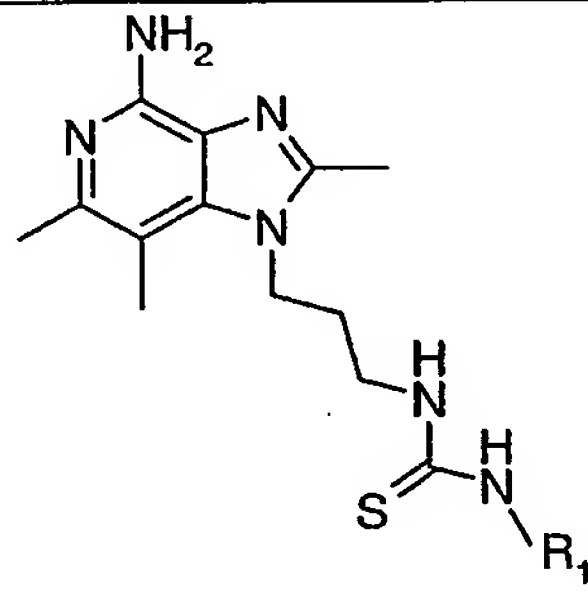
15

The compounds in the table below were prepared using the method of Examples 75 – 85. the appropriate sulfonyl isocyanate was reacted with 1-(3-aminopropyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound.

		
Example Number	R ₁	Accurate Mass (obs.)
88	4-methylphenyl	431.1856
89	2-chlorophenyl	451.1318

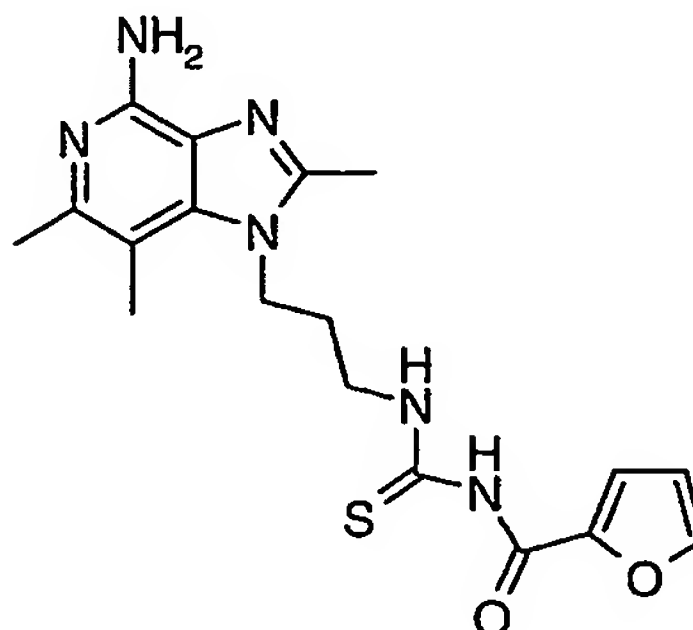
Examples 90 – 92

The compounds in the table below were prepared using the method of Examples 75 – 85. the appropriate isothiocyanate was reacted with 1-(3-aminopropyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound.

		
Example Number	R ₁	Accurate Mass (obs.)
90	phenyl	369.1856
91	2-phenylethyl	397.2186
92	4-methoxyphenyl	399.1980

Example 93

N-[3-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]-*N*'-(2-furoyl)thiourea



5

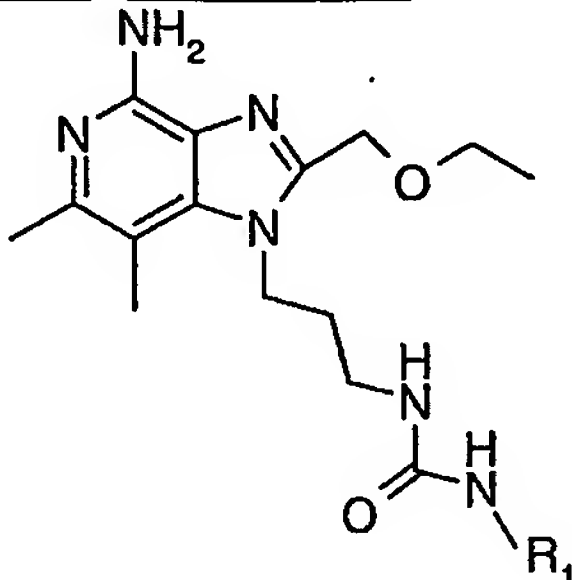
Using the methods of Examples 75 –85, 2-furoylisothiocyanate was reacted with 1-(3-aminopropyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 387.1608.

10

Examples 94 – 106

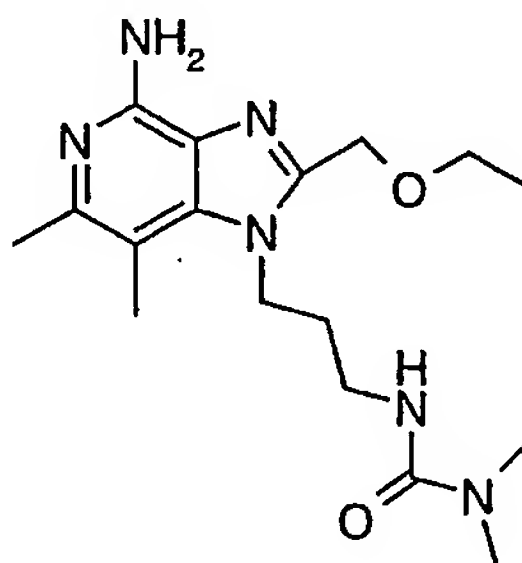
15

The compounds in the table below were prepared using the following method. The appropriate isocyanate(1.1 eq.) was added to a test tube containing a solution of 1-(3-aminopropyl)-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (25 mg; see Example 14 Part C) in chloroform (5 mL). The test tube was capped, vortexed and then placed on a shaker at ambient temperature for ~17 hours. The solvent was removed by vacuum centrifugation. The residue was purified by prep HPLC using the method described above to provide the trifluoroacetate salt of the desired compound. The table below shows the structure of the free base and the observed accurate mass (*m* + *H*).

		
Example Number	R ₁	Accurate Mass (obs.)
94	1-methylethyl	363.2518
95	1,1-dimethylethyl	377.2673
96	butyl	377.2668
97	phenyl	397.2366
98	cyclohexyl	403.2817
99	ethoxycarbonylmethyl	407.2392
100	3-cyanophenyl	422.2321
101	3-methoxyphenyl	427.2458
102	3-acetylphenyl	439.2466
103	4-(dimethylamino)phenyl	440.2788
104	3-(methylthio)phenyl	443.2204
105	4-trifluoromethylphenyl	465.2205

Example 106

N'-{3-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propyl}-*N,N*-dimethylurea

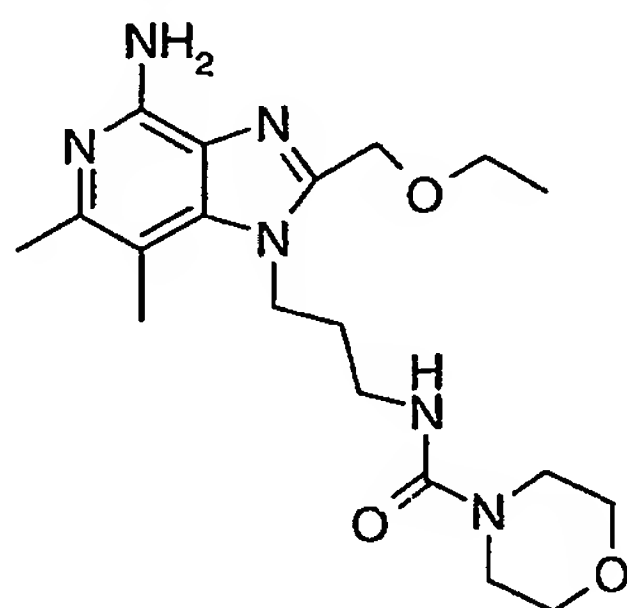


Using the method of Examples 94 – 105, dimethylcarbamyl chloride was reacted with 1-(3-aminopropyl)-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 349.2340.

5

Example 107

N-{3-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propyl}morpholin-4-ylcarboxamide



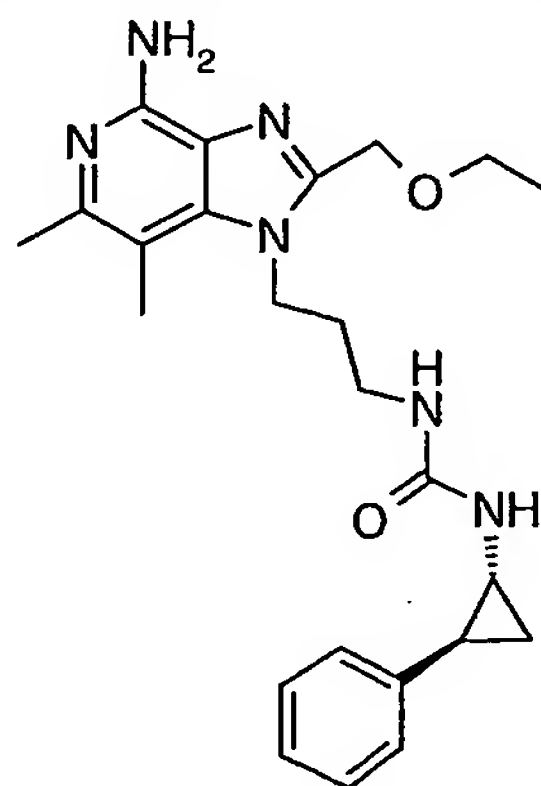
10

Using the method of Examples 94 – 105, 4-morpholinecarbonyl chloride was reacted with 1-(3-aminopropyl)-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 391.2465.

15

Example 108

N-{3-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propyl}-*N'*-[(1*R**,2*S**)-2-phenylcyclopropyl]urea

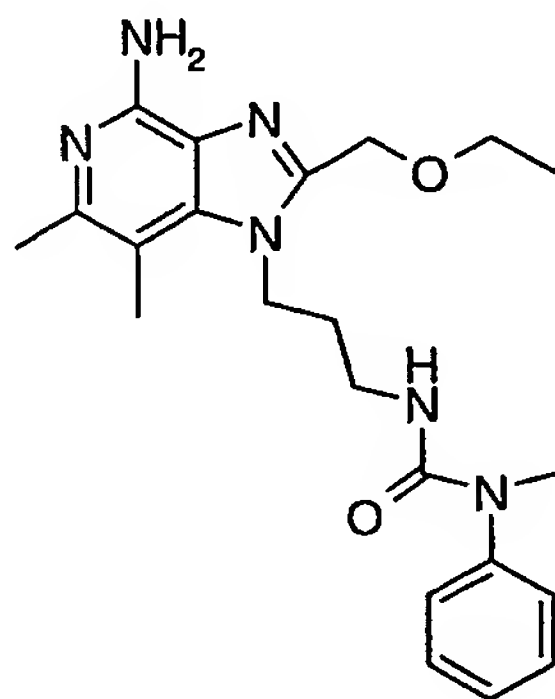


Using the method of Examples 94 – 105, trans-2-phenylcyclopropyl isocyanate was reacted with 1-(3-aminopropyl)-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 437.2674.

5

Example 109

N-[3-(4-amino-2-ethoxymethyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]-*N*-methyl-*N*-phenylurea



10

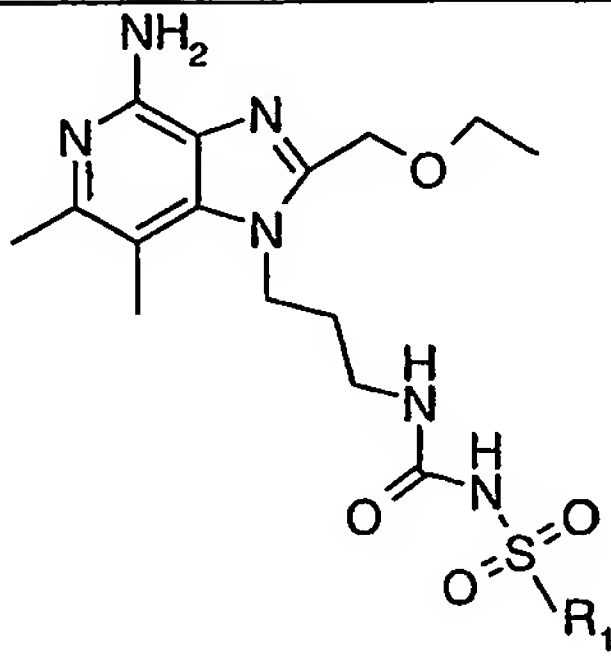
Using the method of Examples 94 – 105, *N*-methyl-*N*-phenylcarbamoyl chloride was reacted with 1-(3-aminopropyl)-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 411.2513.

15

Examples 110 - 112

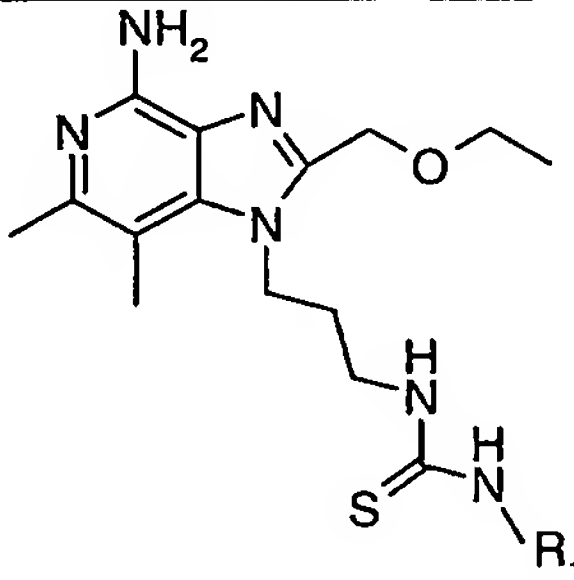
The compounds in the table below were prepared using the method of Examples 94 – 105. The appropriate sulfonyl isocyanate was reacted with 1-(3-aminopropyl)-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound.

20

		
Example Number	R ₁	Accurate Mass (obs.)
110	phenyl	461.1954
111	4-methylphenyl	475.2119
112	2-chlorophenyl	495.1580

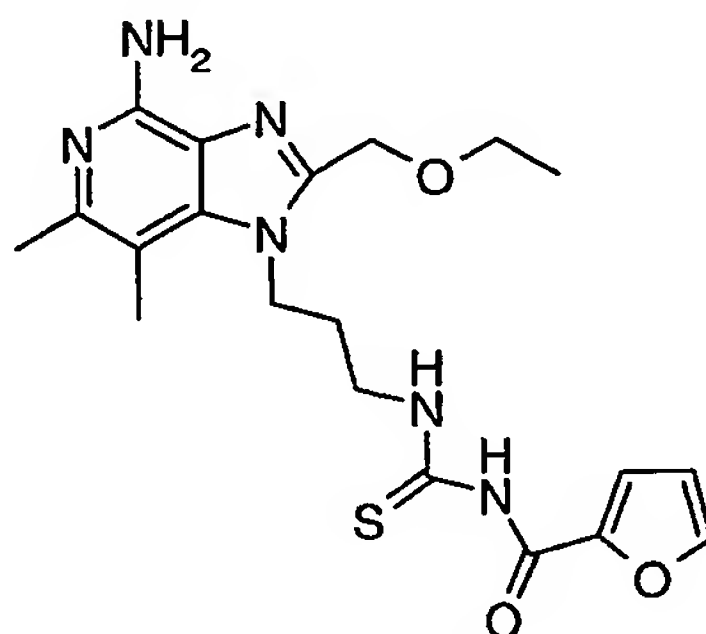
Examples 113 – 116

The compounds in the table below were prepared using the method of Examples 94 – 105. The appropriate isothiocyanate was reacted with 1-(3-aminopropyl)-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound.

		
Example Number	R ₁	Accurate Mass (obs.)
113	3-(diethylamino)propyl	450.3037
114	phenyl	413.2125
115	2-morpholinoethyl	450.2658
116	4-methoxyphenyl	443.2236

Example 117

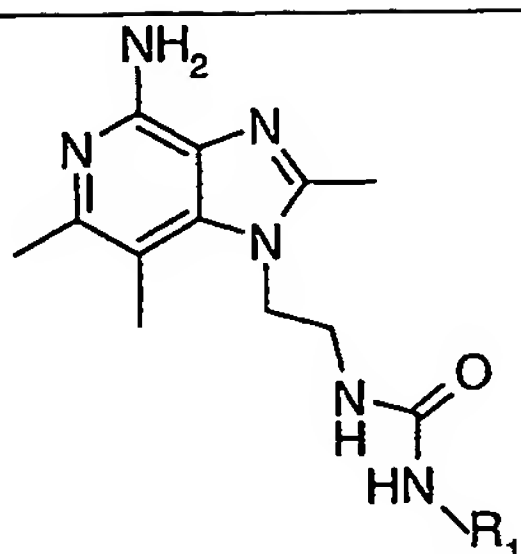
N-[3-(4-amino-2-ethoxymethyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]-*N'*-(2-furoyl)thiourea



Using the method of Examples 94 – 105, 2-furoylisothiocyanate was reacted with 1-(3-aminopropyl)-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 431.1846.

Examples 118 –132

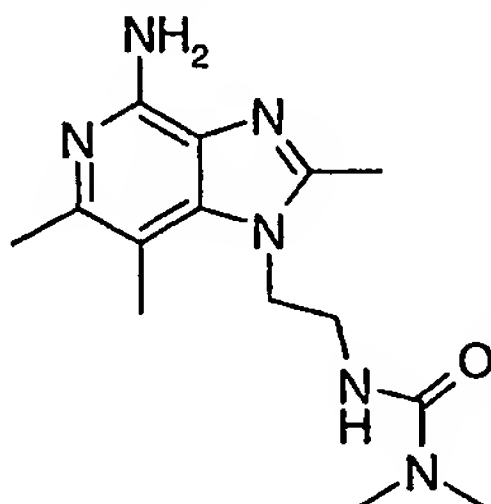
The compounds in the table below were prepared using the following method. The appropriate isocyanate (1.1 eq.) was added to a test tube containing a solution of 1-(2-aminoethyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (20 mg; see Example 15 Part F) in chloroform (5 mL). The test tube was capped, vortexed and then placed on a shaker at ambient temperature for 4 hours. The solvent was removed by vacuum centrifugation. The residue was purified by prep HPLC using the method described above to provide the trifluoroacetate salt of the desired compound. The table below shows the structure of the free base and the observed accurate mass (*m* + *H*).



Example Number	R ₁	Accurate Mass (obs.)
118	1-methylethyl	305.2086
119	1,1-dimethylethyl	319.2244
120	butyl	319.2245
121	phenyl	339.1935
122	cyclohexyl	345.2392
123	ethoxycarbonylmethyl	349.1994
124	3-cyanophenyl	364.1876
125	3-methoxyphenyl	369.2042
126	3-acetylphenyl	381.2048
127	4-(dimethylamino)phenyl	382.2352
128	3-(methylthio)phenyl	385.1805
129	4-trifluoromethylphenyl	407.1812
130	benzoyl	367.1903
131	1-adamantyl	397.2716
132	4-phenoxyphenyl	431.2187

Example 133

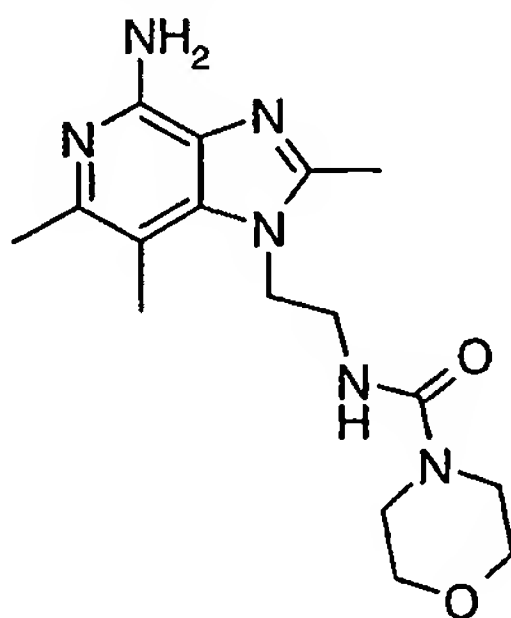
N'-[2-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)ethyl]-*N,N*-dimethylurea



5 Using the method of Examples 118 –133, dimethylcarbamyl chloride was reacted with 1-(2-aminoethyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 291.1929.

Example 134

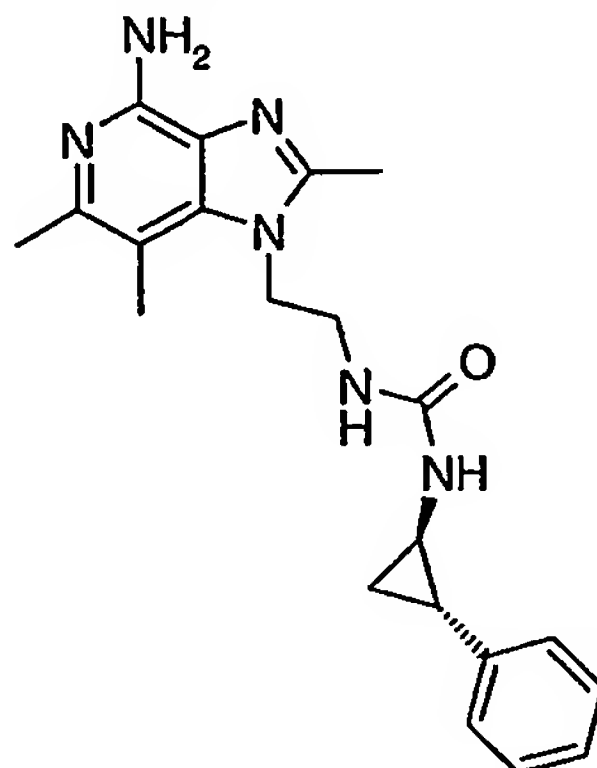
10 *N*'-[2-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)ethyl]morpholin-4-ylcarboxamide



15 Using the method of Examples 118 –133, 4-morpholinecarbonyl chloride was reacted with 1-(2-aminoethyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 333.2025.

Example 135

N-[2-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)ethyl]-*N'*-[(1*R*,2*S*)-2-phenylcyclopropyl]urea



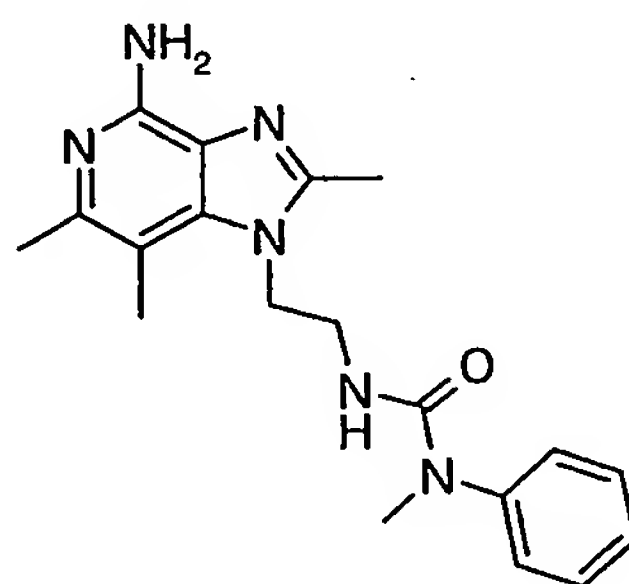
5

Using the method of Examples 118 –133, trans-2-phenylcyclopropyl isocyanate was reacted with 1-(2-aminoethyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 379.2235.

10

Example 136

N'-[2-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)ethyl]-*N*-methyl-*N*-phenylurea

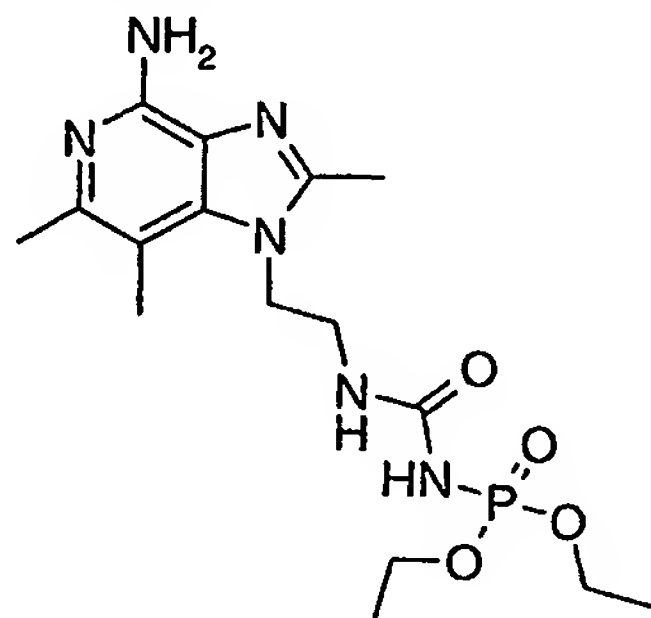


15

Using the method of Examples 118 –133, N-methyl-N-phenylcarbonyl chloride was reacted with 1-(2-aminoethyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 353.2073.

Example 137

diethyl {[2-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)ethyl]amino}carbonylamidophosphate



5

Using the method of Examples 118 –133, diethoxyphosphinyl isocyanate was reacted with 1-(2-aminoethyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 399.1926.

10

Examples 138-139

The examples in the table below were prepared using the method of Examples 118 – 133. The appropriate sulfonyl isocyanate was reacted with 1-(2-aminoethyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound.

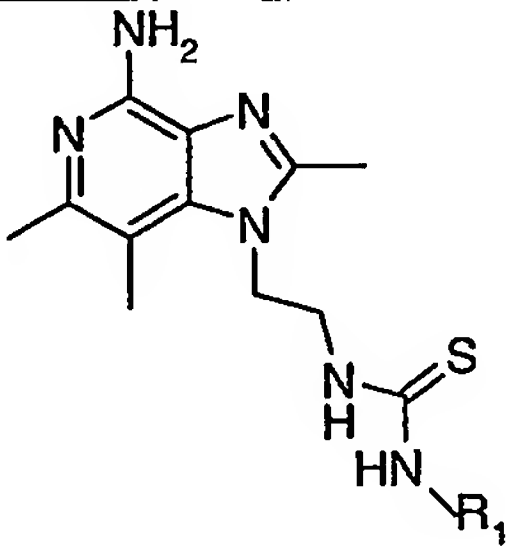
Example Number	R ₁	Accurate Mass (obs.)
138	phenyl	403.1559
139	2-chlorophenyl	437.1158

15

Examples 140 – 146

The examples in the table below were prepared using the method of Examples 118 – 133. The appropriate isothiocyanate was reacted with 1-(2-aminoethyl)-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound.

5

		
Example Number	R ₁	Accurate Mass (obs.)
140	3-(diethylamino)propyl	392.2599
141	phenyl	355.1697
142	2-furoyl	373.1443
143	2-morpholinoethyl	392.2233
144	4-methoxyphenyl	385.1826
145	benzoyl	383.1647
146	1-adamantyl	413.2472

Examples 147 – 164

Part A

10 Propanenitrile (120 mL) was added to malonyl dichloride (100 g) and the reaction mixture was stirred under nitrogen for 24 hours. Dioxane (200 mL) was added. The resulting solid was isolated by filtration, washed with water and suction dried. It was dissolved in methanol (~75 mL) and then combined with dioxane (300 mL). The volume was reduced under reduced pressure until a thick white precipitate formed. The resulting
 15 precipitate was isolated by filtration, washed with dioxane and dried to provide 64.4 g of 6-chloro-4-hydroxy-5-methyl-1*H*-pyridin-2-one hydrochloride as a white solid.

Part B

6-Chloro-4-hydroxy-5-methyl-1H-pyridin-2-one hydrochloride (64 g) was dissolved in sulfuric acid (325 mL) while cooling in an ice bath. Nitric acid was added drop wise over a period of 90 minutes. The reaction mixture was allowed to stir for an additional 30 minutes and then it was poured into ice water (2 L). The resulting precipitate was isolated by filtration, washed with water and then dried to provide 42.5 g of 6-chloro-4-hydroxy-5-methyl-3-nitro-1H-pyridin-2-one as a light yellow solid.

Part C

Triethylamine (30.2 mL, 220 mmol) was added to a cooled (ice bath) suspension of 6-chloro-4-hydroxy-5-methyl-3-nitro-1H-pyridin-2-one (5.0 g, 24.4 mmol) in anhydrous dichloromethane and the starting material went into solution. Triflic anhydride (8.3 mL, 48.9 mmol) was added drop wise. After 1 hour *tert*-butyl 4-aminobutylcarbamate was added. After 1 hour the reaction was allowed to warm to ambient temperature and then left overnight. The solvents were removed under reduced pressure and the residue chromatographed to provide crude 4-({4-[(*tert*-butoxycarbonyl)amino]butyl}amino)-6-chloro-5-methyl-3-nitropyridin-2-yl trifluoromethanesulfonate as a black oil.

Part D

The crude product from Part C was combined with toluene (2 L), triethylamine (25.4 mL), and dibenzylamine (35.5 mL) and heated at reflux for 1 hour. The reaction mixture was allowed to cool to ambient temperature, washed with water (4 x 1 L) and brine (200 mL), dried over magnesium sulfate and then concentrated under reduced pressure to provide 100 g of an orange oil. A portion (70 g) was purified by column chromatography (1200 mL of silica gel eluting with 20/80 ethyl acetate/hexanes) to provide 52 g of *tert*-butyl 4-{{2-chloro-6-(dibenzylamino)-3-methyl-5-nitropyridin-4-yl}amino}butylcarbamate as a light yellow oil.

Part E

Sodium borohydride (0.40 g, 10.6 mmol) was slowly added to a solution of nickel(II) chloride hexahydrate (0.70 g, 2.93 mmol) in methanol (75 mL). After 15 minutes a solution of *tert*-butyl 4-{{2-chloro-6-(dibenzylamino)-3-methyl-5-nitropyridin-4-yl}amino}butylcarbamate (3.25 g, 5.87 mmol) dissolved in a mixture of methanol (25 mL) and dichloromethane (20 mL) was added to the reaction mixture. Sodium borohydride (0.93 g) was slowly added. After 30 minutes analysis by high performance

liquid chromatography indicated that the reaction was complete. The reaction was scaled up to 48.7 g of the starting material using the same conditions. The small and large scale reaction mixtures were combined and filtered through a layer of Celite® filter aid. The filtrate was passed through a plug of silica gel and the plug was washed with 50/50 dichloromethane/methanol. The filtrate was concentrated under reduced pressure to provide 46.3 g of *tert*-butyl 4-{[3-amino-6-chloro-4-(dibenzylamino)-5-methylpyridin-4-yl]amino}butylcarbamate as a light brown oil.

Part F

Triethylamine (12.2 mL) was added to a chilled (0°C) solution of the material from Part E in dichloromethane (300 mL). A solution of ethoxyacetyl chloride (10.8 g) in dichloromethane (100 mL) was added via an addition funnel. The reaction was allowed to warm to ambient temperature overnight. Analysis indicated that some starting material remained so 0.2 eq of the acid chloride was added. After 1 hour the reaction mixture was washed with water (3 x 500 mL), dried over magnesium sulfate and then concentrated under reduced pressure to provide *tert*-butyl 4-{[2-chloro-6-(dibenzylamino)-5-(2-ethoxyacetylamino)-3-methylpyridin-4-yl]amino}butylcarbamate as a brown oil. The oil was dissolved in pyridine (300 mL). Pyridine hydrochloride (40 g) was added and the reaction mixture was heated at reflux for 4 hours. The reaction mixture was allowed to cool to ambient temperature and then it was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (500 mL) and washed with water (500 mL). An emulsion formed and was cleared by adding sodium chloride to the aqueous layer. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to provide 52.1 g of a dark brown oil. This oil was purified by chromatography (silica gel eluting with 30/70 ethyl acetate/hexanes) to provide 24.8 g of *tert*-butyl 4-[6-chloro-4-(dibenzylamino)-2-(ethoxymethyl)-7-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butylcarbamate as a light yellow oil.

Part G

Trifluoroacetic acid (160 mL) was added over a period of 15 minutes to a chilled (0°) solution of the material from Part F in dichloromethane (500 mL). The reaction mixture was allowed to stir overnight and then it was concentrated under reduced pressure. The residue was partitioned between dichloromethane (500 mL) and 10% sodium hydroxide (500 mL). The base layer was extracted with dichloromethane (x 2). The

combined organics were dried over magnesium sulfate and then concentrated under reduced pressure to provide a brown oil. The oil was dissolved in isopropanol (100 mL) and then combined with 41 mL of 1 M hydrochloric acid in diethyl ether. Diethyl ether (200 mL) was slowly added to the mixture. The resulting precipitate was isolated by
5 filtration, washed with ether and dried in a vacuum oven at 80°C overnight to provide 11.25 g of the hydrochloride salt of the desired product as a white solid. The solid was dissolved in water (200 mL), combined with sodium carbonate (15 g), and then extracted with dichloromethane (3 x 500 mL). The combined extracts were dried over magnesium sulfate and then concentrated under reduced pressure to provide 10.2 g of 1-(4-
10 aminobutyl)-N,N-dibenzyl-6-chloro-2-(ethoxymethyl)-7-methyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine as a clear oil.

Part H

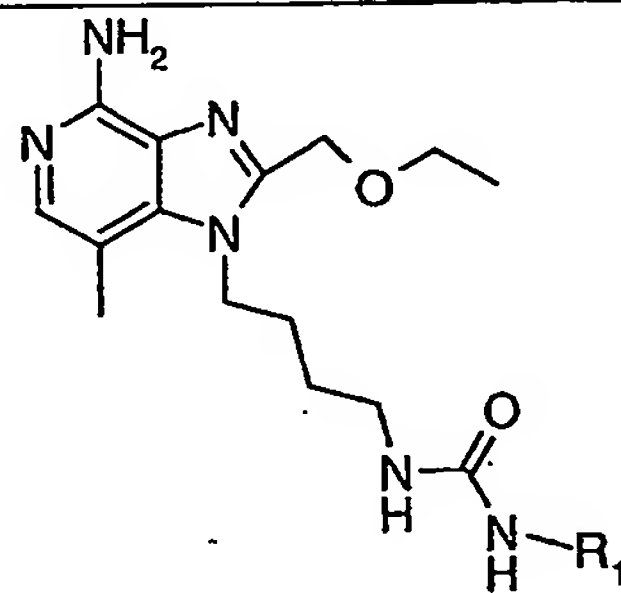
Under a nitrogen atmosphere, ammonium formate (13.7 g) was added to a mixture of 10% palladium on carbon (10 g) and ethanol (200 mL). The material from Part H was
15 dissolved in a mixture of hot ethanol (600 mL) and methanol (400 mL) and then added to the reaction mixture. The reaction mixture was heated at reflux for 4 hours and then allowed to cool to ambient temperature overnight. Analysis indicated that the reaction was only about one half complete so catalyst (5 g) and ammonium formate (5 g) were added and the reaction mixture was heated at reflux for 4 hours. The reaction mixture was
20 allowed to cool to ambient temperature and then it was filtered through a layer of Celite® filter aid. The filter cake was washed with 50/50 ethanol/methanol (1 L). The solvents were removed under reduced pressure to provide a clear oil. The oil was partitioned between dichloromethane (500 mL) and 10% sodium hydroxide (200 mL). The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over
25 magnesium sulfate and then concentrated under reduced pressure to provide 4.30 g of 1-(4-aminobutyl)-2-(ethoxymethyl)-7-methyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine as a clear oil which partially solidified on standing.

Part I

The compounds in the table below were prepared using the following
30 method. The appropriate isocyanate (1.1 eq.) was added to a test tube containing a solution of 1-(4-aminobutyl)-2-(ethoxymethyl)-7-methyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (23.5 mg) in chloroform (5 mL). The test tube was capped and then placed on a

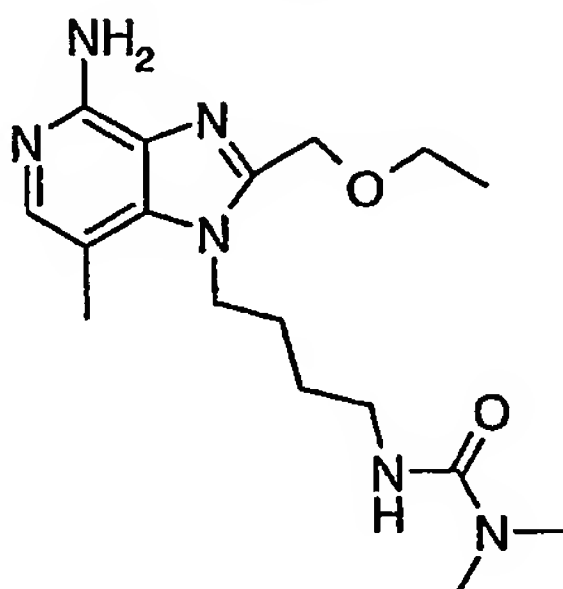
shaker at ambient temperature for 4 hours. The solvent was removed by vacuum centrifugation. The residue was purified by prep HPLC using the method described above to provide the trifluoroacetate salt of the desired compound. The table below shows the structure of the free base and the observed accurate mass ($m + H$).

5

		
Example Number	R ₁	Accurate Mass (obs.)
147	1-methylethyl	363.2528
148	1,1-dimethylethyl	377.2666
149	butyl	377.2674
150	phenyl	397.2359
151	cyclohexyl	403.2818
152	ethoxycarbonylmethyl	407.2393
153	3-cyanophenyl	422.2296
154	3-methoxyphenyl	427.2459
155	3-acetylphenyl	439.2463
156	4-(dimethylamino)phenyl	440.2787
157	3-(methylthio)phenyl	443.2259
158	4-trifluoromethylphenyl	465.2206
159	1-adamantyl	455.3117
160	3-(ethoxycarbonyl)phenyl	469.2549
161	(1-naphthyl)ethyl	475.2790
162	4-phenoxyphenyl	489.2589
163	4-methylphenylsulfonyl	475.2126
164	2-chlorophenylsulfonyl	495.1571

Example 165

N'-{4-[4-amino-2-(ethoxymethyl)-7-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}-*N,N*-dimethylurea



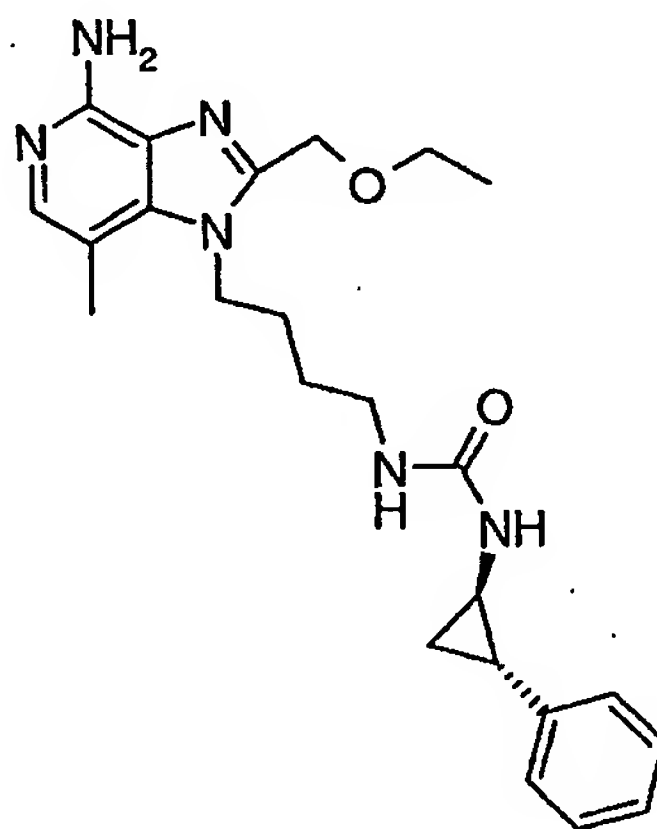
5

Using the method of Examples 147 – 164, dimethylcarbonyl chloride was reacted with 1-(4-aminobutyl)-2-(ethoxymethyl)-7-methyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 349.2334.

10

Example 166

N'-{4-[4-amino-2-(ethoxymethyl)-7-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}-*N*'-[(1*R*,2*S*)-2-phenylcyclopropyl]urea

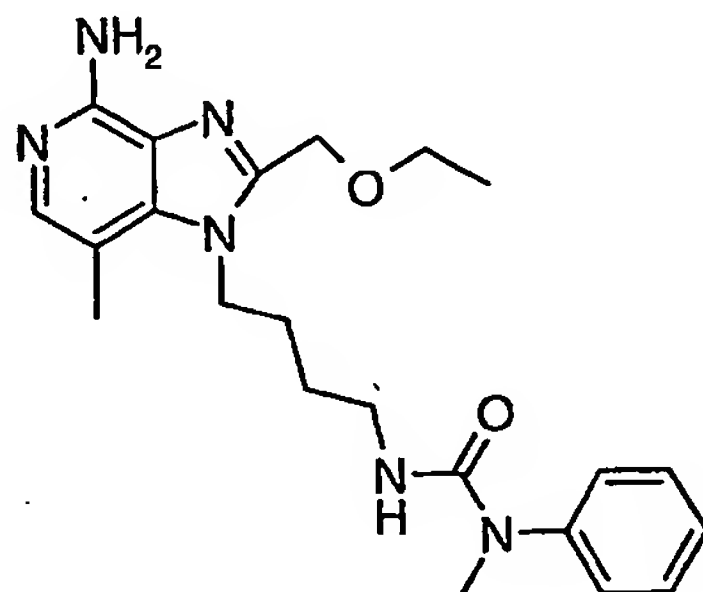


15

Using the method of Examples 147 – 164, trans-2-phenylcyclopropyl isocyanate was reacted with 1-(4-aminobutyl)-2-(ethoxymethyl)-7-methyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 437.2668.

Example 167

N'-{4-[4-amino-2-(ethoxymethyl)-7-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}-*N*-methyl-*N*-phenylurea



5

Using the method of Examples 147 – 164, *N*-methyl-*N*-phenylcarbonyl chloride was reacted with 1-(4-aminobutyl)-2-(ethoxymethyl)-7-methyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound. The observed accurate mass was 411.2532.

10

Examples 168 – 175

The compounds in the table below were prepared using the method of Examples 147 – 164. The appropriate isothiocyanate was reacted with 1-(4-aminobutyl)-2-(ethoxymethyl)-7-methyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine to provide the desired compound.

15

Example Number	R ₁	Accurate Mass (obs.)
168	3-(diethylamino)propyl	450.3007
169	phenyl	413.2129
170	2-furoyl	431.1870
171	2-morpholinoethyl	450.2653
172	4-methoxyphenyl	443.2240
173	benzoyl	441.2090
174	1-adamantyl	471.2902
175	4-sulfamoylphenyl	492.1848

CYTOKINE INDUCTION IN HUMAN CELLS

5 An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et. al. In "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", Journal of Leukocyte Biology, **58**, 365-372 (September, 1995).

10 Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using Histopaque®-1077. Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and

15

resuspended at 4×10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

5 Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μ M.

Incubation

10 The solution of test compound is added at 60 μ M to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (30-0.014 μ M). The final concentration of PBMC suspension is 2×10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated
15 for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (~200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C
20 until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in
25 pg/mL.

Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by Origen® M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human
30 TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

The table below lists the lowest concentration found to induce interferon and the lowest concentration found to induce tumor necrosis factor for each compound. A "*" indicates that no induction was seen at any of the tested concentrations.

5

Cytokine Induction in Human Cells		
Example Number	Lowest Effective Concentration (μ M)	
	Interferon	Tumor Necrosis Factor
1	0.12	1.11
2	0.0046	0.01
3	0.01	0.37
4	0.12	0.37
5	0.01	0.12
6	0.01	0.01
7	0.37	*
8	0.04	10
16	*	*
17	30	*
18	*	*
19	10	30
20	30	*
21	*	*
22	*	*
23	*	*
24	10	30
25	*	3.33
26	30	30
27	*	*
28	*	*
29	*	*
30	*	*

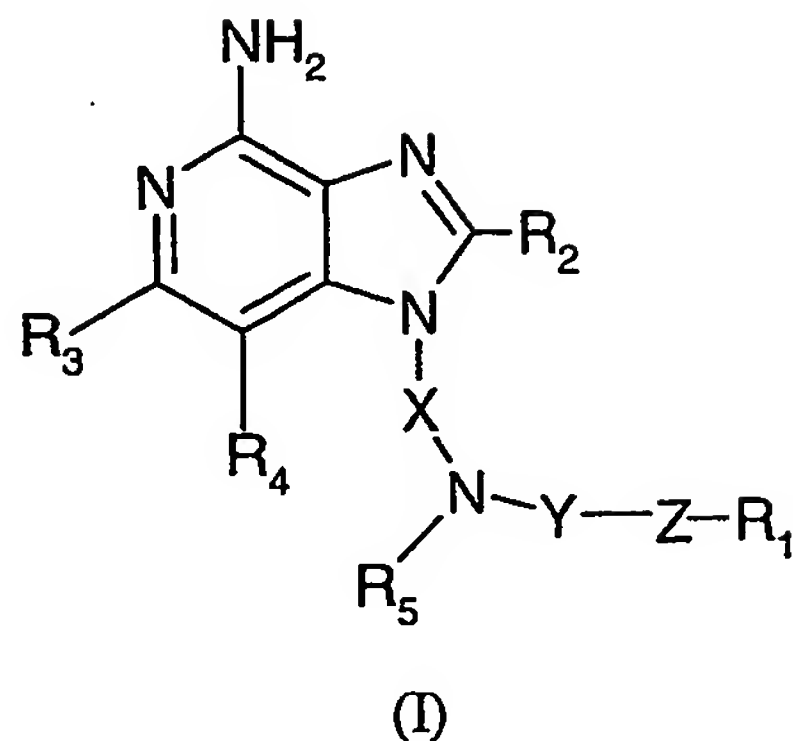
Cytokine Induction in Human Cells		
Example Number	Lowest Effective Concentration (μ M)	
	Interferon	Tumor Necrosis Factor
31	*	*
32	*	*
33	3.33	3.33
34	*	*
35	3.33	30
36	1.11	30
38	3.33	30
39	3.33	10
40	3.33	*
41	10	30
42	10	10
43	0.041	10
44	3.33	10
45	3.33	10
46	3.33	10
47	*	*
48	*	*
49	3.33	30
50	0.37	3.33
51	3.33	10
52	0.37	3.33
53	0.37	3.33
54	1.11	3.33
55	3.33	10
56	1.11	3.33
57	0.37	1.11
58	0.37	3.33
59	1.11	10

Cytokine Induction in Human Cells		
Example Number	Lowest Effective Concentration (μ M)	
	Interferon	Tumor Necrosis Factor
60	0.37	1.11
61	0.37	1.11
62	0.37	1.11
63	0.014	1.11
64	0.37	1.11
65	0.37	1.11
66	1.11	10
67	1.11	3.33
68	0.37	1.11
69	3.33	*
70	10	*
71	0.37	3.33
72	0.37	1.11
73	0.12	1.11
74	0.37	1.11

5 The present invention has been described with reference to several embodiments thereof. The foregoing detailed description and examples have been provided for clarity of understanding only, and no unnecessary limitations are to be understood therefrom. It will be apparent to those skilled in the art that many changes can be made to the described embodiments without departing from the spirit and scope of the invention. Thus, the scope of the invention should not be limited to the exact details of the compositions and
 10 structures described herein, but rather by the language of the claims that follow.

WHAT IS CLAIMED IS:

1. A compound of the formula (I):



wherein

X is alkylene or alkenylene;

Y is $-\text{CO}-$ or $-\text{CS}-$;

Z is $-\text{NR}_6-$; $-\text{NR}_6-\text{CO}-$; $-\text{NR}_6-\text{SO}_2-$; or $-\text{NR}_7-$;

R₁ is aryl, heteroaryl, heterocyclyl, alkyl or

alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-substituted aryl;

-substituted heteroaryl;

substituted heterocyclyl;

-O-alkyl;

-O-(alkyl)₀₋₁-aryl;

-O-(alkyl)₀₋₁-substituted aryl;

-O-(alkyl)₀₋₁-heteroaryl;

-O-(alkyl)₀₋₁-substituted heteroaryl;

- 5
10
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- O-(alkyl)₀₋₁-heterocyclyl;
 - O-(alkyl)₀₋₁-substituted heterocyclyl;
 - COOH;
 - CO-O-alkyl;
 - CO-alkyl;
 - S(O)₀₋₂-alkyl;
 - S(O)₀₋₂-(alkyl)₀₋₁-aryl;
 - S(O)₀₋₂-(alkyl)₀₋₁-substituted aryl;
 - S(O)₀₋₂-(alkyl)₀₋₁-heteroaryl;
 - S(O)₀₋₂-(alkyl)₀₋₁-substituted heteroaryl;
 - S(O)₀₋₂-(alkyl)₀₋₁-heterocyclyl;
 - S(O)₀₋₂-(alkyl)₀₋₁-substituted heterocyclyl;
 - (alkyl)₀₋₁-N(R₆)₂;
 - (alkyl)₀₋₁-NR₆-CO-O-alkyl;
 - (alkyl)₀₋₁-NR₆-CO-alkyl;
 - (alkyl)₀₋₁-NR₆-CO-aryl;
 - (alkyl)₀₋₁-NR₆-CO-substituted aryl;
 - (alkyl)₀₋₁-NR₆-CO-heteroaryl;
 - (alkyl)₀₋₁-NR₆-CO-substituted heteroaryl;
 - P(O)(Oalkyl)₂;
 - N₃;
 - halogen;
 - haloalkyl;
 - haloalkoxy;
 - CO-haloalkyl;
 - CO-haloalkoxy;
 - NO₂;
 - CN;
 - OH;
 - SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R₂ is selected from the group consisting of:

- 5 -hydrogen;
 -alkyl;
 -alkenyl;
 -aryl;
 -substituted aryl;
 -heteroaryl;
 -substituted heteroaryl;
 -alkyl-O-alkyl;
 -alkyl-S-alkyl;
10 -alkyl-O-aryl;
 -alkyl-S-aryl;
 -alkyl-O- alkenyl;
 -alkyl-S- alkenyl; and
 -alkyl or alkenyl substituted by one or more substituents selected
15 from the group consisting of:
 -OH;
 -halogen;
 -N(R₆)₂;
 -CO-N(R₆)₂;
20 -CS-N(R₆)₂;
 -SO₂-N(R₆)₂;
 -NR₆-CO-C₁₋₁₀ alkyl;
 -NR₆-CS-C₁₋₁₀ alkyl;
 -NR₆- SO₂-C₁₋₁₀ alkyl;
25 -CO-C₁₋₁₀ alkyl;
 -CO-O-C₁₋₁₀ alkyl;
 -N₃;
 -aryl;
 -substituted aryl;
30 -heteroaryl;
 -substituted heteroaryl;
 -heterocyclyl;

-substituted heterocyclyl;
-CO-aryl;
-CO-(substituted aryl);
-CO-heteroaryl; and
-CO-(substituted heteroaryl);

5

R_3 and R_4 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio;

10

R_5 is H or C_{1-10} alkyl, or R_5 can join with X to form a ring that contains one or two hetero atoms;

each R_6 is independently H or C_{1-10} alkyl;

R_7 is H or C_{1-10} alkyl which may be interrupted by a heteroatom or when R_1 is alkyl, R_7 and R_1 can join to form a ring;

or a pharmaceutically acceptable salt thereof.

15

2. A compound or salt of claim 1 wherein Y is $-CO-$.

3. A compound or salt of claim 1 wherein Y is $-CO-$ and R_1 is alkyl, aryl or substituted aryl.

20

4. A compound or salt of claim 2 wherein R_2 is alkyl-O-alkyl.

5. A compound or salt of claim 2 wherein R_2 is H or alkyl.

25

6. A compound or salt of claim 1 wherein Y is $-CS-$.

7. A compound or salt of claim 6 wherein Y is $-CS-$ and R_1 is alkyl, aryl or substituted aryl.

30

8. A compound or salt of claim 6 wherein R_2 is alkyl-O-alkyl.

9. A compound or salt of claim 6 wherein R_2 is H or alkyl.

10. A compound or salt of claim 9 wherein R₁ is alkyl, aryl, or substituted aryl.
11. A compound or salt of claim 1 wherein X is $-(CH_2)_{2-4}-$.
12. A compound or salt of claim 1 wherein R₁ and R₇ join to form a ring.
13. A compound or salt of claim 1 wherein R₁ and R₇ join to form a morpholine ring.
14. A compound or salt of claim 1 wherein R₅ and R₆ are both hydrogen.
15. A compound or salt of claim 1 wherein R₃ and R₄ are both methyl.
16. A compound or salt of claim 1 wherein R₃ and R₄ are independently H or alkyl.
17. A compound selected from the group consisting of:
N-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-*N'*-phenylurea;
N-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-*N'*-phenylthiourea;
N-{4-[4-amino-2-(ethoxymethyl)-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}morpholin-4-ylcarboxamide;
N-[4-(4-amino-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]morpholin-4-ylcarboxamide;
2-(ethoxymethyl)-6,7-dimethyl-1-{2-[1-(morpholin-4-ylcarbonyl)piperidin-4-yl]ethyl}-1*H*-imidazo[4,5-*c*]pyridin-4-amine;
N-[3-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]morpholin-4-ylcarboxamide;
N-{3-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propyl}morpholin-4-ylcarboxamide;
N-{2-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]-1,1-dimethylethyl}-*N'*-phenylurea

N-(2-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]-1,1-dimethylethyl)morpholin-4-ylcarboxamide; and

N-[2-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)ethyl)morpholin-4-ylcarboxamide;

5 or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

10 19. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 2 in combination with a pharmaceutically acceptable carrier.

20. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 17 in combination with a pharmaceutically acceptable carrier.

15

21. A method of inducing cytokine biosynthesis in an animal comprising administering a therapeutically effective amount of a compound of claim 1 to the animal.

20 22. A method of treating a viral disease in an animal comprising administering a therapeutically effective amount of a compound of claim 1 to the animal.

23. A method of treating a neoplastic disease in an animal comprising administering a therapeutically effective amount of a compound of claim 1 to the animal.

25 24. A method of inducing cytokine biosynthesis in an animal comprising administering a therapeutically effective amount of a compound of claim 2 to the animal.

25. A method of treating a viral disease in an animal comprising administering a therapeutically effective amount of a compound of claim 2 to the animal.

30

26. A method of treating a neoplastic disease in an animal comprising administering a therapeutically effective amount of a compound of claim 2 to the animal.

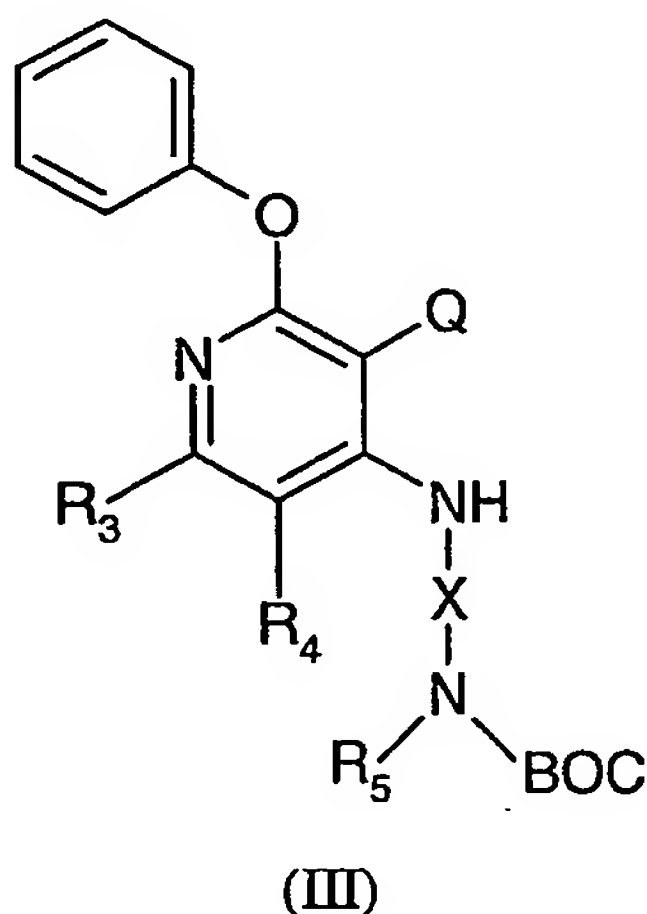
27. A method of inducing cytokine biosynthesis in an animal comprising administering a therapeutically effective amount of a compound of claim 17 to the animal.

5 28. A method of treating a viral disease in an animal comprising administering a therapeutically effective amount of a compound of claim 17 to the animal.

29. A method of treating a neoplastic disease in an animal comprising administering a therapeutically effective amount of a compound of claim 17 to the animal.

10

30. A compound of the formula (III):



15

wherein: Q is NO₂ or NH₂;

X is alkylene or alkenylene;

R₃ and R₄ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio; and

20

R₅ is H or C₁₋₁₀ alkyl, or R₅ and X can join to form a ring that contains one or two hetero atoms;
or a pharmaceutically acceptable salt thereof.

25